UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

EFFICACY OF LOW-INTENSITY PULSED ULTRASOUND IN HEALING OF LOWER LIMB FRACTURES

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A thesis submitted to the Faculty of Health Sciences, School of Therapeutic Sciences, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy.

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DECLARATION

I, Nontembiso Magida hereby declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

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DEDICATION

I dedicate this work to the Lord for protecting me and taking me through to here, and I survived. To my children Atlega and Botlhale, thank you guys, I know I have taken away your time. My niece and deputy parent, Asange Magida, without you this work would not have been a success, thank you for understanding.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

1. Exploring non-union in lower limb fractures in Gauteng Province, South Africa (Oral presentation in 2nd Cape Town International Trauma Conference)
2. Determining factors for the development of a clinical pathway post non-union fractures of the lower limb (Under journal review)
3. Fracture healing using low-intensity pulsed ultrasound in patients with surgically managed lower limb fractures: a randomised control trial (Under journal review)

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ABSTRACT

Introduction, purpose and relevance

Fracture healing represents a worldwide challenge to return to ordinary well-being preceding injury. Fracture healing encompasses multifaceted and progressive events due to the extent of the injury, factors associated with management and patient-related variables. The more complex the injury is, the higher the chances of developing infection and therefore the longer the healing will take. Fracture healing also depends on the surgical management of choice, which normally depends on the severity of the injury and consists of either open reduction internal fixation or external fixation. In addition, patient-related factors have an added impact as to whether the fracture heals or not. Patient-related factors, such as comorbidities including immuno-compromising diseases and health risk behaviours, are known to hinder fracture healing and result in non-union fractures.

The prevalence of lower limb fracture non-union in South Africa is not well documented, as the medical and patient-related factors associated with lower limb non-union fractures in this context have not been reported. It was deemed useful to determine the clinical pathway and the patient outcomes of lower limb non-union fractures in South Africa. The literature revealed that the management of delayed and non-union fractures is problematic and alternative approaches to augment the management of fractures have been growing globally. One form of intervention is low-intensity pulsed ultrasound, which has been studied internationally and reported to be effective in fracture healing. Studies that have been done do not highlight the effect of ultrasound in patients with a high prevalence of comorbidities, including diabetes, hypertension, HIV and health risk behaviours such as smoking. The studies that have investigated the efficacy of LIPUS involved its daily application. The efficacy of low-intensity pulsed ultrasound in lower limb fractures in a South African population with a high prevalence of multiple comorbidities has not been determined. The relevance of the information gathered is to reduce the burden of fracture healing and non-union fractures by using non-invasive equipment such as low-intensity pulsed US that could help some patients with surgically managed fractures with either delayed or non-union fracture healing, which leads to prolonged stay in hospital.

Therefore, the study sought to:

- To determine the prevalence and site of lower limb non-union fractures in hospitals in Johannesburg
- To determine the factors to inform a proposed clinical pathway for patients with lower limb non-union fractures at selected public hospitals in Gauteng
- To determine the effect of non-invasive low-intensity LIPUS on the healing of lower limb fractures

The specific objectives the study were:

1. To establish the prevalence of lower limb non-union fractures at three selected public hospitals in Johannesburg.
2. To determine the factors in forming a proposed clinical pathway for patients with lower limb non-union fractures at the five selected public hospitals in Gauteng, South Africa.
3. To establish the quality of life of patients with lower limb non-union fractures.
4. To establish the effect of <u>low intensity pulsed ultrasound</u> on lower limb fractures including non-union fractures.
5. To establish the influence of demographic, health status variables and smoking on fracture healing.

Methodology

The study includes two phases. The first phase had two parts. Part 1 used a retrospective record review of 3847 records on patients with lower limb fractures, to establish the prevalence of non-union fractures in three academic <u>state</u> hospitals in Gauteng province, South Africa. In Part 2, a cross sectional prospective descriptive study was used to determine medical- and patient-related factors associated with non-union fractures. Data were collected on medical factors, patients' health-related quality of life and impairment in everyday activities to contribute to a proposed clinical pathway for physiotherapy for the treatment of lower limb non-union fractures.

In the second phase was a double-blinded randomised controlled trial, using a consecutive sampling method to recruit patients with lower limb fractures. One hundred and fifteen patients, including 17 with non-union fractures, were recruited on admission from two state academic hospitals and randomly assigned to the control or intervention group, and who received real or sham low-intensity pulsed ultrasound. The researcher confirmed the fracture site from the file and X-rays as diagnosed by the radiologist, before the treatment commenced. Treatment with low-intensity pulsed ultrasound was administered every second day to attain 20 treatments. Both machines were pre-set at an intensity of 0.03 W/cm², frequency of 1.5 MHz and pulse width of 200 µs. The sham machine was set not to produce ultrasound. After the completion of low-intensity pulsed ultrasound treatment, fracture healing was assessed using X-rays for callus formation, cortices bridged, fracture gap and overall healing at six, 12 and 18 weeks. Both the researcher and research assistance providing the intervention and the radiologist who assessed the X-rays were blinded to patient group allocation. The fracture healing outcomes were observed by the radiologist on X-rays. The difference in fracture healing between the intervention and control group was analysed using Pearson's Chi Square test. The percentage change in fracture healing within the intervention and control group was analysed using the McNemar Chi-square test at six, 12 and 18 weeks. Data to determine the association between fracture outcomes and personal and medical demographics, comorbidities and risky health behaviours were analysed using logistic regression and presented as odds ratios and 95% confidence intervals. The logistic regression was used to establish the effect of medical comorbidities on fracture healing in the context of the current study. Data to determine the association between fracture outcomes and personal and medical demographics, comorbidities as well as risk health behaviours were analysed using logistic regression and presented as odds ratios and 95% confidence intervals.

Results and Discussion

The results for Phase 1, Part 1 indicated a low prevalence of less than 1% (0.72%; n=28) for fracture non-union. Non-union was more prevalent in males than in females in the 41-60 age group. The low prevalence was attributed to the exclusion criteria used in this phase of the study. The exclusion criteria included patients with pathological fractures, and multiple fractures on the ipsilateral side.

However, even in Phase 1, Part 2 of the study, where inclusion criteria were widened, only 22 participants were recruited at five state hospitals in Gauteng over an 11month period. Participants were between 20 and 59 years, unemployed or dependent on a social grant. A high percentage of participants in this study were HIV positive (41%), and 13% had diabetes, while all of them smoked. Medical factors determined a long stay in hospital, a number of re-admissions, medical and surgical procedures, medication, rehabilitation therapies, as well as assistive devices. All participants had impairment in everyday activities and decreased quality of life. A clinical pathway for physiotherapy treatment of patients with non-union fractures was created considering these factors.

In Phase 2 of the study, the participants between the ages of 18 and 82 years, again presented with a high prevalence of comorbidities, HIV positive (43%), 27% had diabetes and 61% of them smoked. Results indicated no significant difference in fracture healing for patients with surgically managed lower limb fractures who received real and sham low-intensity pulsed ultrasound for any period up to 18 weeks. Some acceleration in fracture healing was found for a small percentage of the experimental group, and this group has less deterioration in fracture healing over 18 weeks than did participants in the control group. A significant difference was found for the participants with non-union fractures treated with real low-intensity pulsed ultrasound compared to those treated with sham low-intensity pulsed ultrasound.

Fracture healing in the logistic regression for single factors was found to be associated with gender, the site of fracture, fracture management and non-union, while multivariate regression analysis showed that gender, type of fracture management, non-union and HIV were associated with fracture healing.

Conclusion

Fracture non-union and the outcomes of non-union fractures are of concern in patients treated in state hospitals in South Africa. There are considerable costs in terms of medical and rehabilitation care, as well as to the patient in terms of accessing care. Patients face a prolonged period in which no fracture healing is reported and present with decreased health-related quality of life and functional impairment. In view of the high prevalence of comorbidities associated with non-union fractures, we proposed a clinical pathway for physiotherapy, which in turn suggested that the use of low-intensity pulsed ultrasound might be useful in facilitating fracture healing.

While low-intensity pulsed ultrasound cannot be recommended for the treatment of surgically managed lower limb fractures in patients in state hospitals in Gauteng, it may be recommended for patients with non-union fractures. A significant difference in terms of fracture healing was seen for patients with non-union fractures who received low-intensity pulsed ultrasound every second day for 20 days of treatment. However, this recommendation must be viewed in light of the small sample size of patients with non-union fractures and the costs and challenges of providing this intervention.

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OPERATIONAL DEFINITIONS

Clinical pathways - are a common component in the quest to improve the quality of health and are used to reduce variation, improve quality of care, and maximise the outcomes for specific groups of patients through these improvement initiatives. They aim to organise and standardise care processes, thus maximising patient outcomes and improving organisational efficiency (Rotter et al., 2010)

Comorbidities: a single core concept: the presence of more than one distinct condition in an individual used as a person-level construct which considers the nature of the health condition, the relative importance of the co-occurring conditions and the chronology of presentation of the conditions (Valderas et al., 2009).

Health risk factors: is a variable associated with an increased risk of disease or infection in relation to the current health state and the likelihood of future health outcomes (Abate et al., 2013).

Low-intensity pulsed ultrasound - is a form of ultrasound that is delivered at a much lower intensity to induce regenerative and anti-inflammatory effects on biological tissues, such as bone (Watanabe et al., 2010)

Non-union fractures – a non-union fracture is characterised by pain and functional disability. A non-union fracture is a fracture that is at least nine months old and has not shown signs of healing for at least three consecutive months (Calori et al., 2017)

ABBREVIATIONS

ART – Anti-retroviral therapy

BMD – Bone mineral density

CHBAH – Chris Hani Baragwanath Academic Hospital

CMAH – Charlotte Maxeke Academic Hospital

GEE - Generalised estimating equation

HIV - Human immunodeficiency virus

HJH – Helen Joseph Hospital

HRQoL – Health-Related Quality of Life

ICF – International Classification of function, disability and Health

ITT – Intention-To-Treat

IQR – Interquartile range

KAH – Kalafong Academic Hospital

LIPUS – Low-intensity pulsed ultrasound

MCS – Mental Component Score

PCS – Physical Component Score

SBAH – Steve Biko Academic Hospital

SF-36 – Short Form 36

CHAPTER 1: INTRODUCTION

1.1 BACKGROUND AND NEED

Fracture healing represents a global challenge for patients and healthcare practitioners. The challenge branches from the restorative method, which takes six to eight weeks and is added by restrictions in daily activities (Liu et al., 2014; Mundi et al., 2009). This challenge becomes extreme when healing is delayed, or when there is no union at all. Healthcare practitioners need to investigate the causes of delayed union or non-union to have the ability to achieve greater medical alternatives or treatment choices to speed up fracture healing. Delayed fracture healing escalates costs, not only to the affected individual but also to the Department of Health (Nandra et al., 2016; Panteli et al., 2015). Delayed fracture-healing marks in added challenges to the patient that may include potential increased dangers of incapacity (Zura et al., 2017). Additionally, loss of occupation due to lengthy sick leave taken off work, loss of earnings (Nandra et al., 2016), increased liability on the family due to functional dependency and psychosocial problems due to the conditions the patient finds themselves in (Iseselo et al., 2016) is also as results of tardy fracture healing.

In Physiotherapy, therapeutic ultrasound has been used since the 1940s to relieve pain, to reduce muscle spasm and to improve muscle strength, which in turn promotes healing. <u>The application of ultrasound for therapeutic effects was known to carry risks of adverse effects which may lead to hazardous injuries (Miller et al., 2012). On some of the adverse effects that LIPUS was associated with is skeletally immature bones, which is not contra-indicated (de Gusmão, Alves, Belangero, 2016) as at lower intensity (0.5 W/cm2) there are no adverse effects on bone growth (Warden et al., 2006).</u> Ultrasound is also contra-indicated straight over metal implants as it may cause risks burns (Kocaoğlu et al., 2011). A survey of opinions and performs was conducted and found that surgeons felt that ultrasound was contra-indicated and harmful to healing fractures, or that it was of no use. The authors established that 20.5% of physiotherapists conveyed that ultrasound was contra-indicated and was, or may be, damaging to healing bones (Busse and Bhandari, 2004).

<u>Studies have shown that the impact of ultrasound on fracture healing depends on the intensity used (Watanabe et al., 2010). The low-intensity dose (0.5W/cm2) and high-</u>

intensity dose (2.2 W/cm2) in rabbit growth plate were compared (Lyon et al., 2003). The results in the higher dose group were that 3-6 cases showed destruction of the distal femoral epiphysis and blocking of the proximal tibial plateau, as well as unclear growth plate lines (Lyon et al., 2003).

Low-intensity pulsed ultrasound (LIPUS) has been used to speed fracture healing. Low doses of ultrasound had no contrary effect on bone growth in the short-term follow-up. LIPUS has been used to quicken fracture healing and has been proven effective (Lou et al., 2017; Morshed, 2014).

Fracture healing involves numbered range of measures to repair injured bone to normal. Satisfactory blood supply and mechanical strength are necessities for bone healing (Marsell and Einhorn, 2011). Marsell and Einhorn (2011) further stated that the first step of fracture healing is the progress in haematoma formation, which employ the healing response; blood thickens to form a clot then the immediate ends of the fractured bone are disadvantaged of their nutrition, as the osteocytes are gone (Ponemone et al., 2016). Bone remodelling require elimination of old or impaired bone by osteoclast and the continuous bone growth made possible by osteoblasts (Feng and McDonald, 2011).

The periosteal cells proximal to the fracture gap and fibroblasts develop into chondroblast, few days after the fracture, and that forms cartilage (Huang et al., 2008). The dense fibrous membrane covering the surfaces of bones, away to the fracture gap advance into osteoblasts, which form intertwine bone (Marsell and Einhorn, 2011). These two tissues unite with their equivalents and end into a new form of diverse tissues called fracture callus, which restores some of its original strength. Once the fracture ends are connected by soft callus, the hard callus stage begin and continues until the wreckages are definitely amalgamated by new bone (Slutsky and Herman, 2005). Hard callus starts marginally and gradually travels near the centre of the fracture (Casanova et al., 2014). The final stage of healing begins when the fracture has solidly amalgamated with woven bone. The lamellar then gradually substitutes the woven bone.

Many known factors affect fracture healing. Features affecting fracture healing are sub-grouped into injury-related and patient-related factors (Hernandez et al., 2012a). Injury-related factors include the type of bone fractured. Cancellous bone heals quicker than cortical bone (Han et al., 2015). In cancellous bone, fracture healing demonstrates less failure of the blood supply, compared to cortical bone (Han et al., 2015). Delayed healing occurs due to displaced and comminuted fractures, as normally the soft tissue is trapped in the gap and bridging of the cortices delayed. (Kostenuik and Mirza, 2017). Blood vessels at the fracture site are interfered by excessive mobility of the fracture (McRae and Esser, 2008). A swelling of clotted blood causes a strain through the tissues and interrupts the callus formation (Marsell and Einhorn, 2011). Other studies further stated that there are also patient-related factors, which include age, nutrition, drug therapy comorbidities, such as bone pathology, diabetes, HIV and smoking, which may decrease fracture healing (Hernandez et al., 2012a; Perazzo et al., 2016).

Patient-related factors highlighted in the literature are relevant to the South African population (Mirhadi et al., 2013). South Africans are affected by deprived diet, which drops the speed of healing (Karpouzos et al., 2017). Diabetes, HIV and smoking may ruin the blood supply and delay fracture healing and these are prevalent in the South African communities (Ferreira et al., 2016b). Nicotine from smoking impedes vascular ingrowth and early restoration of perfusion of the bone and lessens osteoblast role (Daffner et al., 2012). Delayed fracture healing and non-union fractures have been conveyed in patients who smoke (Hernigou and Schuind, 2013; Patel et al., 2013; Pearson et al., 2016). Delayed fracture healing in smokers has been supported by a meta-analysis of 7500 procedures, which exposed that cigarette smokers have a greater chance of delayed and/or non-union of their fractures (Pearson et al., 2016). The findings of the study expressed that smokers have 2.2 (1.9 to 2.6) times the chances of getting tardy and/or non-union when compared to healthy individuals (Pearson et al., 2016).

Non-union fractures are classified as hypertrophic and atrophic, of which in atrophic there is no evidence of callus formation (Rupp et al., 2019; Stewart, 2019). The authors described atrophic non-union fractures as a results of poor healing of bones like impaired blood supply to the bone fragments diabetes or smoking.

Low bone mineral density (BMD) is reported prevalent in HIV positive patients (ChiţuTişu et al., 2016; Kruger and Nell, 2017). The causes of low BMD in patients with HIV infection appears to be dependent on number of factors and represents a collaboration between the HIV infection, osteoporosis risk-factors and the antiretroviral therapy (ART) (McComsey et al., 2010b). The authors concluded that chronic inflammation, and possibly the virus itself, disturbs osteoclast movement of reabsorbing the bone. Several studies expressed that ART is thought to contribute to bone density loss (Duncan and Brown, 2010; Hileman et al., 2015; Ofotokun et al., 2016), however, the underlying pathophysiology is unknown. Any inequality between bone resorption and bone development causes loss of bone density, therefore creating a greater risk of fracture (Kruger and Nell, 2017). The combination of bone development to bone resorption controls suitable stability (Feng and McDonald, 2011).

There are more chances of sluggish healing and non-union in HIV positive patients and increased evidence of a relationship between HIV infections and reduced fracture healing (Richardson et al., 2008). HIV infection accounts to cause imbalance in the amounts of those cytokines involved in the fracture healing and thus seems to harm blood supply of the bone (Richardson et al., 2008). Other possible causes of disturbed fracture healing among people with HIV is the compact body mass index (BMI), suboptimal nutrition, and the effects of anti-retroviral drugs (Richardson et al., 2008).

As HIV progresses, it disrupts the connection amongst bone formation and reabsorption resulting in a net loss of BMD (Kruger and Nell, 2017). HIV infection obscures open fractures by cumulative incidence of infection in fractures and especially in open wounds (Fernandes et al., 2015; Harrison, 2009). HIV may adversely affect fracture union and the changed inflammatory reaction of the immune-compromised patient (Guo and DiPietro, 2010; Harrison et al., 2016).

Several studies have demonstrated accelerated fracture healing using low-intensity pulsed ultrasound (LIPUS) (Dijkman et al., 2009a; Martinez de Albornoz et al., 2011; Martínez-Mesa et al., 2016; Miyabe et al., 2010; Mundi et al., 2009). Ultrasound waves are said to excite bone tissue restoration by causing small, exact pressures in the bone cells, which increases blood flow in the area and mobilises calcium (Yang et al., 2010). Ultrasound uses high-frequency acoustic waves (Miller et al., 2012), rather than electromagnetic energy (O’Brien and William, 2007). Non-thermal effects of ultrasound decrease oedema by growing cell membrane and vascular wall permeability, blood flow, protein synthesis, and tissue regeneration, and that will encourage the healing process (Yang et al., 2017). Early callus mass occurs and results in, but not necessarily, an increased volume of callus (Morgan et al., 2014). Low intensity pulsed ultrasound exposure has been shown to cause increased bone mineralisation (Harrison et al., 2016; Martinez de Albornoz et al., 2011) and an increased rate of callus remodelling (Cheung et al., 2011).

LIPUS is measured in megahertz (MHz) and represents the number of waves (in millions) occurring in one second (O'Brien Jr, 2007). The frequency ranges from 0.75 - 3.3 MHz, the higher the frequency the less the emerging sound beam diverges, thus, low-frequency US produces a more widely diverging beam than high-frequency US, which produces a collimated beam (Reid, 1993). A 1.0 MHz is transmitted through superficial tissues and absorbed primarily in deeper tissues at depths of 3-5 cm or greater (Hayes et al., 2004). The high frequency 3 MHz machine provides treatment to superficial tissue and tendons and penetrates between 1-2 centimetres (Hayes et al., 2004). The low distribution depth is linked with the partial transmission of energy, rapid absorption of energy, and a higher healing amount in a relatively limited tissue depth (O'Brien and William, 2007).

Although LIPUS has been proven to accelerate fracture healing both clinically and practically in a population with mixed comorbidities, the efficacy of LIPUS has been omitted. In a World Health Organization update (De Onis et al., 2006), it was stated that 68% of the world's HIV/AIDS population resides in sub-Saharan Africa. The WHO further explained that in HIV endemic areas, between 16-30% of trauma patients requiring surgery are HIV positive (De Onis et al., 2006). At the Johannesburg hospital trauma unit, in South Africa, the prevalence of HIV positive patients who attended for major surgery was above 30% (Black et al., 2019; Lukhele, 2011). The WHO confirmed these findings in their 2011 to 2013 statistics of the cause of death in South Africa. In 2011, about 17 338 (3.4%) of patients died from HIV/AIDS and 21 147 (4.1%) from diabetes. The numbers are increasing every year. In 2013, there were 23 203 (5.1%) of patients who died from HIV/AIDS and 22 196 (4.8%) from diabetes-related complications (World Health Organisation, 2013). Considering the above facts, the South African population is different from other countries where

LIPUS was studied, and undertaking a study on the effects of LIPUS on fracture healing would add to the knowledge of its effect.

LIPUS has been used as an addition to accelerate fracture healing (Mundi et al., 2009). It has been established that LIPUS accelerates fracture healing in rats with diabetes mellitus, with enhanced mechanical properties of the fracture callus regardless of its poor effect on cellular proliferation (Harrison et al., 2016; MartínezMesa et al., 2016; Gebauer et al., 2002a). However, the study was done on animals and not human beings with diabetes. The current study sought to study the efficacy of LIPUS in a South African population with mixed comorbidities. The addition of comorbidities made the study different to what had already been done in other countries.

1.2 PROBLEM STATEMENT

In South Africa, there is an epidemic of musculoskeletal trauma and HIV infection (Kasipersad et al., 2009). The aforementioned affect both the economically young and active, and elderly people. South Africa is a developing country with rapid urbanisation and on-going socio-economic deprivation. In an urgent endeavour to better their lives, people from previously disadvantaged groups may engage in risky physical activities and lifestyles. In the process, traumatic musculoskeletal injuries occur and because of decreased immunity from the HIV infection and the other comorbidities, this leads to delayed or non-union of the fractures.

The impact of LIPUS on the healing of fractures has been established in populations with no comorbidities. Participants in previous studies were taught how to use the machine at home and the application of LIPUS treatment was done daily. This study sought to establish the effect of LIPUS on callus formation within eight weeks of its application on alternate days. This study aimed to find ways to accommodate the South African population in reduced treatment time and frequency, and compare the healing of surgically managed fractures in the presence of comorbidities between those treated with and without LIPUS.

1.3. RESEARCH QUESTIONS

The study sought to answer the following research questions:

- What is the prevalence of non-union lower limb fractures in patients in public hospitals in Johannesburg?
- What factors inform a proposed clinical pathway and outcomes of non-union lower limb fractures in patients at selected public hospitals in Johannesburg, South Africa?
- What are the effects of non-invasive low-intensity pulsed ultrasound on fracture healing?

Null hypothesis

Non-invasive low-intensity pulsed ultrasound does not accelerate fracture healing.

Alternate Hypothesis

Non-invasive low-intensity pulsed ultrasound can significantly accelerate the fracture-healing process and increase the callus index.

1.4 AIMS OF THE STUDY

The aim of the study was:

- <u>To determine the prevalence and site of lower limb non-union fractures in selected hospitals in Johannesburg</u>
- <u>To determine the factors that inform and to establish a clinical pathway for patients with lower limb non-union fractures at selected public hospitals in Gauteng</u>
- <u>To determine the effect of non-invasive low-intensity LIPUS on the healing of lower limb fractures</u>

1.4.1 Objectives of the study

The objectives of the study were:

1. To establish the prevalence of lower limb non-union fractures at three selected public hospitals in Johannesburg

2. To determine the factors that inform and to establish a clinical pathway for patients with lower limb non-union fractures at the five selected public hospitals in Gauteng, South Africa
3. To establish the quality of life of patients with lower limb non-union fractures
4. To establish the effect of LIPUS on lower limb fractures including non-union fractures
5. To establish the influence of demographic, health status variables and smoking on fracture healing.

1.5 SIGNIFICANCE OF THE STUDY

Non-invasive low-intensity pulsed ultrasound treatment may enhance the mechanical properties of fracture callus formation and reduce the healing time of fractures. Reducing the fracture healing time and aiding the fracture to heal satisfactorily may reduce or minimise associated disability and socioeconomic costs for patients and improve their quality of life. Additionally, understanding any difference in the effects of low-intensity pulsed ultrasound in a subset of immune-suppressed patients and patients with open wounds will contribute to an area where little is known.

1.6 RESEARCH SITE

The study was conducted at five hospitals in Gauteng, South Africa. Phase 1 was conducted at Chris Hani Baragwanath Academic Hospital (CHBAH), a large referral and central hospital, Charlotte Maxeke Academic Hospital (CMAH) and Helen Joseph Hospital (HJH) in Johannesburg, South Africa.

Chris Hani Baragwanath Academic Hospital is the third-largest hospital in the world and is the largest in the southern hemisphere. The hospital has 3400 beds of which 232 are orthopaedic beds (Government Gazette 2012; Pillay and Ramokgopa, 2013). The hospital is situated in the Soweto, south of Johannesburg, South Africa. It is one of the 40 Gauteng provincial hospitals and is financed and managed by the Gauteng

Provincial Department of Health. It is a teaching hospital for the University of the Witwatersrand Medical School, along with the CMAH and HJH. The Charlotte Maxeke Academic Hospital (formerly Johannesburg General Hospital) is an accredited general hospital in Parktown, Johannesburg, Gauteng; it has 1088 usable beds (Government Gazette 2012) and the hospital's professional and support staff exceeds 4000 people. It is also the main teaching hospital for the University of the Witwatersrand, Faculty of Health Sciences, and provides the service base for undergraduate and post-graduate training in all areas of health professions. The hospital offers a full range of tertiary, secondary and highly specialised services. A National Tertiary Services Grant, as well as a Provincial Allocation, funds the costs of providing these services to the population of Gauteng Province, in addition to the neighbouring provinces. The hospital serves as a referral hospital for a number of hospitals in its referral chain (Gauteng Department of Health, 2017a).

Helen Joseph Hospital is a government public hospital with the sole responsibility of providing tertiary healthcare services to the community of Gauteng. In order to achieve this responsibility, the hospital relies heavily on the commitment and competency of its ethical and naturally caring employees. Helen Joseph Hospital, renamed on 1st April 1997 to reflect the transformation in the country following the advent of democracy in 1994, is a tertiary hospital, part of the Wits University circuit responsible for teaching healthcare workers and the provision of tertiary health services. The hospital has 485 beds with 1886 staff, is situated in Auckland Park, Johannesburg, and provides services to a region with a population of approximately 11 488 424 (Gauteng Department of Health, 2018a).

Data for Phase 2 of the study was collected at Steve Biko Academic (SBAH) and Kalafong Academic Hospitals in Pretoria, Gauteng. The Steve Biko Academic Hospital is a purely tertiary healthcare institution, rendering specialised and highly specialised services to medically referred patients; it is a referral hospital in that patients are referred to the institution by their local clinics. It has 832 beds and is affiliated with the University of Pretoria (Gauteng Department of Health, 2018b).

Kalafong Hospital is a public hospital in Pretoria, Gauteng. The hospital is situated on the western outskirts of Pretoria in the suburb of Atteridgeville, consists of 857 beds and is affiliated with the University of Pretoria (Gauteng Department of Health, 2017b).

1.7 OUTLINE OF THE THESIS

A gap was identified in the research available on patients with lower limb non-union fractures being treated in state hospitals in Gauteng, South Africa. Very limited research is available on the prevalence of non-union fractures in the context of these hospitals, as well as the medical, therapeutic and personal factors related to the outcomes for these patients. The study was completed in two phases in order to address the gap in research in terms of prevalence, factors related to treatment and patient-related factors associated with lower limb non-union fractures. The effect of non-invasive treatment in the form of LIPUS was then considered in relation to fracture healing in the lower limb including non-union fractures.

The worldview for this research study included positivism and pragmatism. In mixed methods research, it is common to have more than one worldview and this study was of a quantitative nature, with variables that could be measured, and which were associated with positivism or realist worldview relating to hypotheses (Creswell and Plano Clark 2018). The main outcome of this study was to establish the reality of the effectiveness of LIPUS intervention on surgically treated lower limb fractures Pragmatism, as a worldview, was included to accommodate findings of other outcomes that require exploration so all singular and multiple perspectives in this mixed methods research methodology would be considered (Creswell and Plano Clark 2018).

A mixed methodology approach was used to answer the objectives of this thesis as stated below (Figure 1.1).

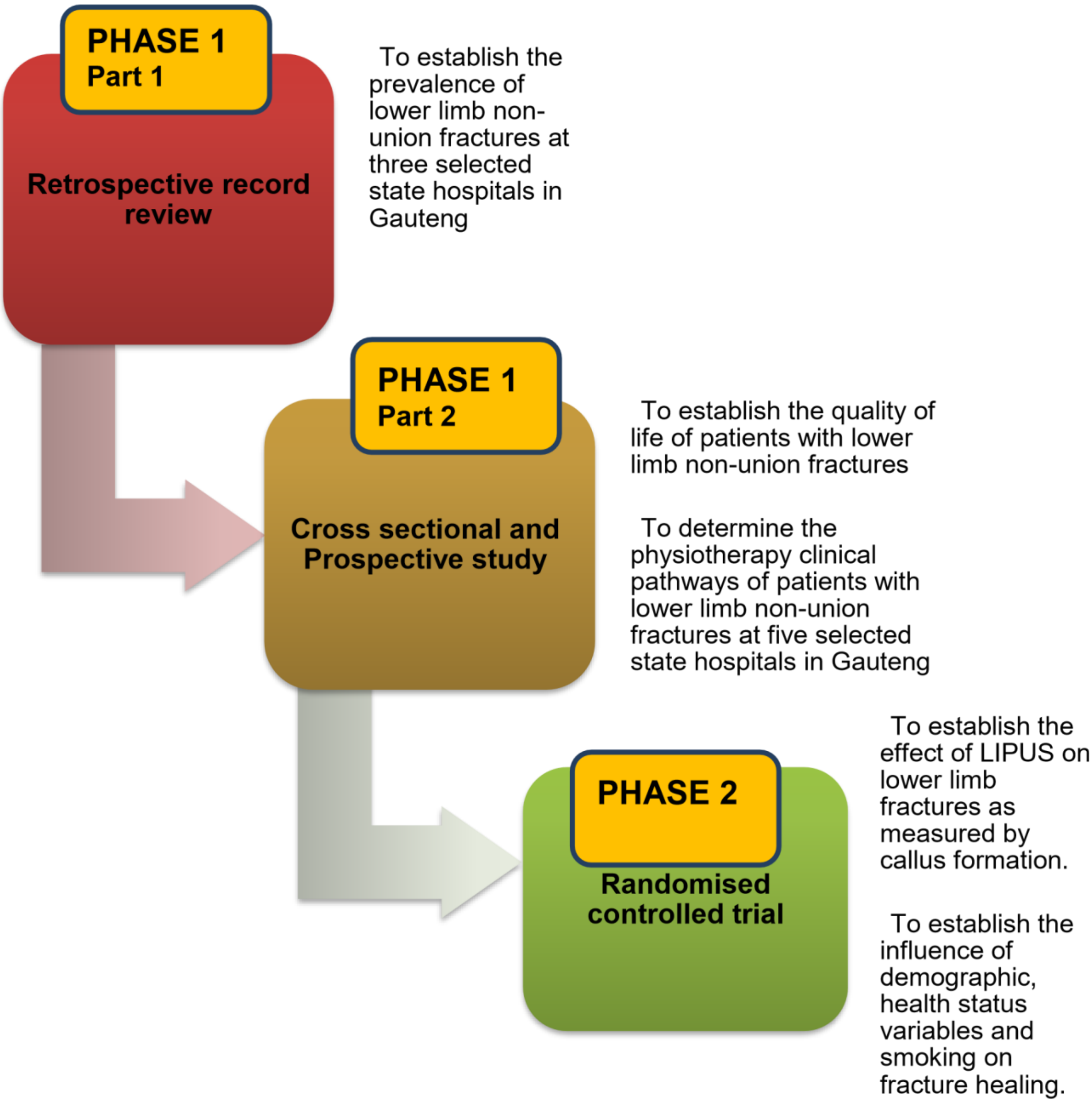

Figure 1.1 Outline of the mixed methodological approach

Phase 1 Part 1 of the study determined the prevalence of lower limb non-union fractures in three state hospitals in Gauteng. Understanding the site and prevalence of non-union fractures, and the demographics of patients with non-union fractures was important as these needed to be considered in relation to international research and any differences identified. This part of Phase 1 also helped as background information so that settings for Part 2 could be selected to achieve a sample of patients with non-union fractures.

In Part 2, the medical- and patient-related factors associated with lower limb non-union fractures were determined. Data were collected on medical factors including the length of stay in hospital, a number of readmissions, medical and surgical procedures, medication, rehabilitation therapies as well as assistive devices. Patient-related factors associated with non-union fractures including demographics, comorbidities and health-related risk factors, as well as the patients' health-related quality of life and impairment in everyday activities were considered. With evidence for physiotherapy treatment from the literature, this information contributed to a proposed clinical pathway for physiotherapy for the treatment of lower limb non-union fractures. Data from this part of the study confirmed a high prevalence of comorbidities and health-related risk factors amongst patients with lower limb non-union fractures. The proposed clinical pathway pointed to the use of LIPUS, based on reported evidence in the literature for facilitating healing and treating delayed healing of lower limb non-union fractures, which may be associated with these comorbidities and health-related risk factors.

Phase 2 of the study, therefore, considered the application of the LIPUS in a sample of patients in two state hospitals with surgically managed lower limb non-union fracture, including patients with diagnosed non-union fractures. A double-blinded randomised controlled trial, using a consecutive sampling method to recruit patients with lower limb fractures, was used and patients were randomly assigned to either control or intervention group who received a real or sham low-intensity pulsed ultrasound. Fracture healing was assessed using X-rays for callus formation, cortices bridged, fracture gap and overall healing at six, 12 and 18 weeks.

1.7.1 Layout of the thesis

Chapter 1: Introduction

This chapter provided background to fracture healing and lower limb non-union fractures as well as the use of LIPUS in the intervention of non-union fractures. Aims and objectives of the research were also stated.

Chapter 2: Literature review

This chapter reviews the literature on fracture healing locally and internationally, including demographic, medical factors related to lower limb fractures as well as management and conservative management of fractures. The effect of comorbidities and health risk factors are considered. Conservative management of fractures using LIPUS and differences as to the effectiveness are reviewed.

Chapter 3: Phase 1 Part 1: Exploring non-union in lower limb fractures in Gauteng Province, South Africa

This chapter explored the prevalence of lower limb non-union fractures in Gauteng. Records of 3842 patients with lower limb fractures were reviewed one year prior**;** 28 patients had non-union fractures and the majority were males.

Chapter 4: Phase 2 Part 2: Factors informing the development of a clinical pathway and quality of life post non-union fractures of the lower limb.

This chapter highlighted demographics, health status and current clinical practice related to patients with lower limb non-union fracture. Male patients had more health-related status than females and their quality of life was poor due to non-union fractures. Functional outcomes and health-related quality of life of patients with lower limb fracture non-union after a six-month follow up period was also determined. All the patients had poor functional outcomes after the six months in a prospective study.

Chapter 5: Phase 2: Fracture healing of patients with lower limb fractures managed with low-intensity pulsed ultrasound

This chapter discussed efficacy of low-intensity pulsed ultrasound in lower limb fracture healing using a blinded randomised controlled trial. Patients were treated with real LIPUS in the intervention group and sham LIPUS in the control group. The results showed no significant effect of LIPUS on fracture healing except for a small sample of participants who presented with lower limb non-union fractures. Logistic regression indicated a number of factors including HIV are associated with delayed fracture healing in patients treated in state hospitals in Gauteng. The limitations and strengths of the study are presented.

Chapter 6: Conclusion

This chapter presents the main findings of the study as well as the recommendations and clinical implications of the findings.

CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

This literature review aimed to map the key concepts constructing efficacy of LIPUS in fracture healing. This review also aims to gather the main sources and types of evidence done concerning the effectiveness of LIPUS in fracture healing.

In this chapter, the incidence and prevalence of lower limb fractures will be discussed. The healing process of the fractures and complications of non-union fractures and its effect on patient and healthcare systems will also be discussed. The effect of HIV, diabetes, smoking and other comorbidities on fracture healing and clinical pathways of patients with non-union fractures will be explored. Furthermore, the use of LIPUS to accelerate fracture healing and measuring bone healing following fractures will be examined.

A wide variety of search engines including ‘Google scholar’, ‘Medline’ ‘Cinahl’ ‘Pubmed’ and reference lists of the searched articles were used. Studies with randomised controlled trials were preferred, but studies with different designs were also used. Selected studies were reviewed and those conducted on lower limbs were preferred. Outcome measures in the studies observed were time to heal, functional outcome and/or adverse effects. <u>The articles that were reviewed were from the years 2000 to 2020.</u> The animal studies were excluded, except for two animal studies related to high intensity ultrasound versus low-intensity ultrasound, because this study may not be done on animals as a trial.

2.2 INCIDENCE AND PREVALENCE OF LOWER LIMB FRACTURES

There is a perception that the prevalence of fractures in South Africa is high but there is no data available to support or refute that perception. Lower limb fractures report for roughly one-third of all the fractures globally (Kaye and Jick, 2004). The author identified 32 900 subjects who had a first time diagnosis of lower limb fractures within 12 months, with an incident rate of 17% higher in women than in men (Kaye and Jick, 2004). In the epidemiology of lifestyle fracture in England, lower limb fractures were more prevalent in women (37.7%) than in men (33.3%), however, this target population consisted of adults 55 years and older (Scholes et al., 2014). These results highlight a high prevalence in the elderly, while supporting a higher incidence rate in females (Kaye and Jick, 2004). A 10-year nationwide survey was conducted in Taiwan, where an 11.07% incident rate of lower limb fractures was found, with 60% being males and 40% females (Pan et al., 2014). In Brazil, 1200 patient files were evaluated according to incidence of lower limb and hipbone fracture, of which 28.6% female patients and 71.4% male patients' files were analysed (de Andrade Rodrigues et al., 2012). An incidence rate of 0.93 and 2.35 for female and male patients respectively was established (de Andrade Rodrigues et al., 2012). In the aforementioned study, they included hip fractures, which are ilium, ischium and pubis in their definition, whereas in this study, we only looked at the lower limb fractures, excluding the pelvic bone. In India, a retrospective study of prevalence of lower limb fractures was conducted over a period of four years and 1050 cases were ascertained (Jindal et al., 2016); male patients were more prevalent (61.9%) compared to females (38.1%).

Some studies highlighted an increased incidence rate of lower limb fractures in males than in females (Pan et al., 2014; Rodriguez-Merchan et al., 2013). However, prevalence rate has also been reported as being equal in males (Jindal et al., 2016) and females (Scholes et al., 2014). Therefore, fracture healing and the factors that may influence this are important to be recognised.

Incident rate by age was observed more in those above 70 years of age both in males (n=120) and females (n=78) (Jindal et al., 2016). Another study identified that males aged above 50-79 years were more prevalent to lower limb fractures, while in women the lower limb fractures were more prevalent in those older than 80 years (Rodriguez Merchan et al., 2013). These reported results could be because males at 50 years are still very active, participating in traumatic activities, compared to women, hence more incidence and prevalence. Fragility above 80 years of age in females is also contributed to hormonal changes hence increased incidence and prevalence rates (Lunenfeld and Stratton, 2013).

The incidence of fractures was found to be distributed by anatomical sites and it was discovered that the femur was a common site of fractures especially in males (255) than in females (94) (Jindal et al., 2016; Amin et al., 2014). Jindal et al. (2016)'s study generalised the femur as the site of fractures whereas Scholes et al. (2014)

highlighted the exact area of the femur as the femoral shaft, which is more prevalent in males (1.7%) than in females (1.4%). However, tibia/fibula fractures were more prevalent in the study by Scholes et al. (2014), with males higher (10.6%) than females (9.9%). In the study by Rodrigues et al. (2012), tibia/fibula fractures were more prevalent (22.8%) in males between the ages of 30-50 years and femur fracture (15.5%) in those above 50 years. It is highlighted that the incidence and prevalence of lower limb fractures is more in males than in females. The incidence and prevalence distribution by anatomical region is greater in males than females aged below 50 years, and the most common site of fracture was the tibia/fibula followed by the femur (de Andrade Rodrigues et al., 2012). Femur fractures are more prevalent in females aged 70 years or older, which may be supported by the fragility fractures due to osteoporosis, and hormonal changes post menopause (Sözen et al., 2017).

2.3 HEALING PROCESS POST FRACTURES

Fracture healing happens logically after traumatic bony interruption. This course starts with haemorrhage and advancements through three stages: inflammatory, reparative and remodelling (Bahney et al., 2019). This process can be supported by various treatment options with immobilisation. Depending on the fracture site and patient’s age, normal healing may take between 3-12 weeks (Kostenuik and Mirza, 2017). Initial fracture healing is only likely when the bone fragments are re-aligned anatomically, and the fracture area is detained firmly by a suitable fixation without a gap between the bony ends (Marsell and Einhorn, 2011).

An inflammatory response is triggered within few days of injury and finalises up to seven days after fracture (Harwood et al., 2010). The author further clarified that the advantage of this stage is to help immobilise the fracture by causing pain so the patient may protect the injury and inflammation to prevent the patient from moving the area (Harwood et al., 2010). Platelets re-activated deliver an adversely charged surface in areas in which the clotting cascade is instigated, resulting in regulation of mediators vital to current haemostatic responses (Palta et al., 2014; Smith et al., 2015). Injury to the soft tissues and degranulation of platelets results in the discharge of dominant cytokines that yield a typical inflammatory response, that is, vasodilatation and hyperaemia, migration and proliferation of polymorphonuclear neutrophils, macrophages, and others (Zhang and An, 2007; Sprague et al., 2019). Haematoma serves as a source of signalling molecules that recruit cellular events crucial to fracture healing (Marsell and Einhorn, 2011; Schell et al., 2017). A stable immune response is vital for proper bone healing but in delayed fracture healing oestrogen-deficiency impacts the early inflammatory phase of the fracture (HaffnerLuntzer et al., 2017). This entire course generates a reparative granuloma, and known as an external callus.

The reparative phase consists of revascularisation and bone formation by both intramembranous and endochondral pathways, preceding remodelling to restore the normal bone structure (Marsell and Einhorn, 2011). The reparative phase happens within the first few days, prior the inflammatory phase diminishes, and continues for numerous weeks (Lieberman and Friedlaender, 2005). The outcome of this phase is the enhancement of a reparative callus tissue in and about the fracture site, which will ultimately be exchanged by bone (Lieberman and Friedlaender, 2005). The main function of the callus is to develop mechanical stability of the area by supporting it laterally. Osteocytes located at the fracture ends become lacking in nutrients and perish, which is observed by the existence of blank gaps spreading for some distance away from the fracture (Shapiro, 2008). Damaged periosteum and marrow, as well as other surrounding soft tissues, may also contribute to necrotic tissue at the fracture site (Davis et al., 2015). Though these tissues are being resorbed, mesenchymal cells start to create added cells such as fibroblasts, chondroblasts, and osteoblasts (Lieberman and Friedlaender, 2005). These cells may originate in injured tissues, while others migrate to the site with the blood vessels (Alberts et al., 2002). During this phase, the callus can be composed of fibrous connective tissue, blood vessels, cartilage, woven bone, and osteoid (Panteli et al., 2015). As repair advances, the pH progressively turns into neutral and then marginally alkaline, which is ideal for alkaline phosphatase movement and its action in the mineralisation of the callus (Lieberman and Friedlaender, 2005). It has been shown that the earliest bone forms from the cells in the cambium layer of the periosteum. The arrangement of restoration tissue and rate of repair may differ subject on where the fracture happens in the bone, the extent of soft tissue damage, and mechanical stability of the fracture site (Einhorn and Gerstenfeld, 2015). Intramembranous ossification commences within the initial days of fracture, but the proliferative accomplishments seem to stop two weeks after the fracture (Lieberman and Friedlaender, 2005). Osteoblast activity in the woven bone is shown first, as disparate to the cortex within a few millimetres from the fracture site (Lieberman and Friedlaender, 2005). Bone formation in this area occurs by the differentiation of osteoblasts directly from precursor cells, without the formation of cartilage as middle step (Rutkovskiy et al., 2016). The region of this type of bone formation occurring in the external callus is often referred to as the hard callus.

Whereas intramembranous ossification is occurring, cartilage is formed in the margin of the callus, where lower oxygen tension exists (Hadjiargyrou and O'Keefe, 2014; Lieberman and Friedlaender, 2005). Homogeneous cells from the periosteum and adjacent peripheral soft tissues are also seen in the granulation tissue over the fracture site (Hadjiargyrou and O'Keefe, 2014). These cells become larger, start to take on the presence of cartilage, and initiate to synthesise an avascular basophilic matrix, as it is seen in the proliferating zone of the growth plate (Hellings et al., 2016). The area of leathery tissue and fresh cartilage is stated to as the soft callus, and ultimately, the cartilage will substitute all fibrous tissue (Lieberman and Friedlaender, 2005). During the following week of fracture healing, cartilage overlay the fracture site and calcification starts by the route of endochondral ossification (Lieberman and Friedlaender, 2005). The process is similar to the one seen in the growth plate. Neutral proteoglycanases are concealed by hypertrophic chondrocytes first because high levels of glycosaminoglycans are revealed to hinder mineralisation (Lieberman and Friedlaender, 2005). As the mineralisation course continues, the callus solidifies becoming more firm and the fracture site is considered immobilised (Marsell and Einhorn, 2011). Vessels from contiguous bones occupy the calcified cartilage, accumulating the oxygen tension (Lieberman and Friedlaender, 2005). Ultimately, the remodelling process begins after the callus is composed of woven bone, which connects the two fracture ends (Marsell and Einhorn, 2011).

“The remodelling phase is the final phase in fracture healing and begins with the replacement of woven bone by lamellar bone and the resorption of excess callus. Although this phase represents the normal remodelling activity of bone, it may be accelerated in the fracture site for several years. Remodelling of fracture repair after all woven bone is replaced consists of osteoclastic resorption of poorly located trabecular and formation of new bone along lines of stress. The result of the remodelling phase is a gradual modification of the fracture region under the influence of mechanical loads until optimal stability is achieved, where the bone cortex is typically similar to the architecture it had before the fracture occurred" (Marsell and Einhorn, 2011: p552).

2.4 NON-UNION FRACTURES

The Food and Drug Administration (FDA) defines non-union as established when a minimum of nine months has elapsed with no visible progressive signs of fracture healing (Calori et al., 2017). The definition of non-union fracture is controversial. Non-union is explained as the lack of the radiographic development of healing between the third and sixth month after injury (Harwood et al., 2010).

Non-union is a fracture that has no likelihood of healing without supplementary intrusion. Various efforts were taken to lessen the amount of disturbed fracture healing but although the exact osteosynthesis, which is required, and new improved interlocking plates, biologic osteosynthesis and better surgical techniques, such as subcutaneous plating, the inclusive amount has not been reduced (Zimmermann and Moghaddam, 2010). Non-union fractures are one of the reported causes of morbidity and causes a noteworthy drain on a country's assets (Mills and Simpson, 2013). The cost of treating non-union fractures is between £7000 to £79000 per case in the United Kingdom (UK) (Mills and Simpson, 2012).

In Nigeria, with its delicate economy, the economic costs of non-union fractures and consequent treatment puts direct pressure on the economic viability of the households (Ikpeme et al., 2013). This is because there is no social support and universal insurance system to help alleviate the financial burden of the treatment. Several authors classified non-union fractures as hypertrophic and atrophic, of which with atrophic fractures there is no evidence of callus formation (Rupp et al., 2019; Stewart, 2019). The authors explained atrophic non-union fractures as often due to impaired bone healing, for example due to vascular causes (e.g. impaired blood supply to the bone fragments) or metabolic causes (e.g. diabetes or smoking) (Rupp et al., 2019; Stewart, 2019); patients who smoke have a higher incidence of non-union. Hypertrophic non-union fracture is described as a fracture with evidence of callus formation but no union of the bone segments (Stewart, 2019).

The most common type of complication resulting in readmission was non-union (Dunlop et al., 2016). Non-union fracture denotes to a fracture that will not restore without further surgical or non-surgical intervention (usually within 6–9 months) (Calori et al., 2014). With fluctuating healing times for individual fractures and healing possibilities of patients, there is no standard explanation for fracture non-union (Nandra et al., 2016). Non-union is a severe barrier of a fracture and may occur when the fracture is not stable, has limited blood supply or gets infected (Calori et al., 2014).

Non-union is a fracture that has no opportunity of healing without additional management. Several efforts have been completed to decrease the degree of fracture healing but notwithstanding the correct osteosynthesis, which is compulsory, and amended interlocking plates, biologic osteosynthesis and enhanced surgical techniques, such as subcutaneous plating, the overall frequency has not been reduced (Zimmermann and Moghaddam, 2010). Non-union of the fracture is one of the chief reasons of ill health and generates a noteworthy burden on a country's resources (Mills and Simpson, 2012). In Nigeria, with its fragile economy, the economic costs of non-union fractures and consequent treatment puts direct pressure on the economic viability of the households (Ikpeme et al., 2013). This is because there is no social support and universal insurance system to help alleviate the financial burden of the treatment.

There is an amplified frequency of delayed healing and non-union fractures in HIV positive patients and evidence of a relationship between HIV infections and deprived fracture healing. HIV infection is identified as a reason for instability in the stages of cytokines involved in fracture healing (Harrison, 2009; Richardson et al., 2008). Another study reported a risk of increased risk of infection in HIV positive patients (Wijesekera et al., 2016). Infection on the fracture increases chances of poor or delayed healing; therefore, non-union may occur (Mills et al., 2017).

In summarising, non-union fractures are multifactorial and may delay healing and or lead to non-union fractures. Risks of non-union fractures are patient and medical dependent. Resources to diminish non-union fractures are stagnant.

2.5 THE RISK FACTORS AFFECTING NON-UNION FRACTURES

2.5.1 Patient-related factors

Several risk factors are associated with fracture healing outcomes, and provide an on-going clinical challenge for the treatment of fractures (Harrison et al., 2016). Delayed fracture consolidation can be due to age, gender, fracture type and smoking.

2.5.1.1 Smoking

Smoking has been shown to have a disadvantageous influence on delayed healing. There are 4000 chemicals found in cigarettes (Moravej-Salehi et al., 2015). Nicotine, carbon monoxide and hydrogen cyanide are often cited as the causes of the adverse effects (Al-Hadithy et al., 2012). Nicotine in cigarettes ruins the body's small blood vessels, which disturb the body's flow (Moravej-Salehi et al., 2015). Smoking may also have an effect on bone-making cells, osteoblasts, which lay down bone in arranged layers that add strength to the matrix and bone-removal cells, osteoclasts, which remove bone by dissolving the mineral and breaking down the matrix in a process called bone resorption (Tanaka et al., 2013). After injury, the site of fracture is surrounded by activated thrombocytes and their aggregates (Serbest et al., 2016). Nicotine affects blood coagulation by growing platelets aggregation, causing the thickness of blood in the small vessels and a generalised drop in microvascular perfusion (Pamukcu et al., 2011). Platelet collections localise about the sites of fracture where intergranular growth factor is released to recruit cells (Leblanc and Peyruchaud, 2016). Effective fracture healing is highly dependent on tightly controlled mechanisms that are directly involved in the expansion of fibroblast-rich granulation tissue (Martin and Nunan, 2015). Cigarette smoking is thought to influence and exacerbate these pathobiological processes, and increase levels of calcitonin, which in turn lowers calcium levels, making bone formation less possible in fracture healing (Al-Bashaireh et al., 2018). Fracture rates in smokers tend to be higher due to increased skeletal fragility (Hernigou and Schuind, 2013). Smokers have a 40% improved period to union and a chance of non-union compared to non-smokers (Al-Hadithy et al., 2012).

Carbon monoxide plays a damaging role in impairing tissue oxygenation by binding haemoglobin and displacing oxygen molecules, thereby reducing the delivery of oxygen to peripheral tissue (Bender et al., 2014). Another study suggested that hypoxia hindered callus and bone remodelling at late stages of fracture healing (Lu et al., 2008). Hydrogen cyanide found in tobacco chiefly inhibits with oxidative absorption at the cellular levels (Lee et al., 2013). The toxic effects of hydrogen cyanide on the mitochondrial respiratory chain are responsible for hypoxia, which delays the callus formation (Abate et al., 2013). Smoking is associated with an open fracture and is a predictive factor of non-union for all anatomical sites (69% of non-unions) compared to closed fractures without tobacco (21% of non-unions) (Hernigou and Schuind, 2013). Smoking reduces local blood supply and delays healing (Mirhadi et al., 2013).

2.5.1.2 Age

The physiological process of ageing is highly complex at the molecular, cellular, and systemic levels (Povoroznyuk et al., 2014). The production of bone, whether during development or repair, entails the generation of new blood vessels to support the tissue (Tomlinson and Silva, 2013). This data suggests that regardless of the age, reparation goes according to a general scheme but stage-timing recovery is shifted (Povoroznyuk et al., 2014). Balanced inflammatory response is considered vital for proper bone healing (Claes et al., 2003). Oestrogen-deficiency is found to be one of the problems affecting the inflammatory response to fracture healing (Haffner Luntzer et al., 2017). Oestrogen deficiency increases cytokine production around the bone and this interrupts bone turnover and leads to bone resorption (Aydin et al., 2014). However, another study found that patients with healed fractures (age 75.0 ± 12.7 SD) were older ($p < 0.0001$) than patients with non-union (age 69.2 ±13.4 SD) (Zura et al., 2017). Several studies supported the latter and reported that time to union was not predicted by age (Morshed, 2014; Taormina et al., 2014; Zura et al., 2017).

In young adults, non-union rates are frequently reported and are associated with high-energy trauma (Schwartsmann et al., 2015). The young adult rate of non-union peaked in the 35-44-year age bracket in another prospective study (Mills et al., 2017). High-energy trauma is associated with soft tissue injuries (Nandra et al., 2016) comminuted and/or multiple fractures, hence the type of fracture also has an impact on non-union fractures.

2.5.1.3 Type of fracture

The tibia is known as the most fractured lower limb bone in high-energy trauma (Antonova et al., 2013. Non-union fractures in patients with open tibia shaft fractures frequently occur compared to those with closed fractures (Antonova et al., 2013). The author further stated that open fractured patients often have additional fractures within a few years, even if situated elsewhere in the body (Antonova et al., 2013). Local blood damage is associated with diaphyseal non-union in open fractures (Ma et al., 2016). Vascular compromise is the leading risk of non-union fractures in tibial shaft fractures (Elniel and Giannoudis, 2018).

2.5.2 Healthcare related effects

There is a wide range of healthcare management and repeated surgical interventions that non-union fractures require compared to the normal healing fractures (Antonova et al., 2013a). The author emphasised the high cost of care in non-union fractures that included surgical, physiotherapy, medication management and the length of hospital stay (Antonova et al., 2013a).

The use of non-steroidal anti-inflammatory drugs (NSAIDs) and opioids is related with danger of non-union fractures (Zura et al., 2016). Another review added that these NSAIDs are one of the most commonly prescribed drugs for pain relief and inflammation to date (Pountos et al., 2012). However, they impede cyclooxygenase (COX) enzyme activity and drop prostaglandin production, which may have a negative effect in the inflammatory phase of fracture healing (Ferreira et al., 2016b). Another study in joint and bone surgery highlighted that NSAIDs destructively impact blood flow across the fracture gap (Gaston and Simpson, 2007). However, Pountos et al. (2014) concluded in their critical analysis study that there is no clinical or scientific evidence to discard NSAIDs as an anti-inflammatory and pain medication for patients with fractures. The authors however recommended that they should be used with caution, as the findings were more in animal studies, which have different physiological mechanisms to humans. These NSAIDs were given following pain and inflammation prominent from surgical management, which is also accompanying with the risk of non-union (Zura et al., 2016).

Fracture management requires reduction, maintenance of reduction (immobilisation), and rehabilitation. Surgical intervention has been suggested as one of the management types that may inadvertently increase non-union fracture occurrence (Ferreira et al., 2016a). The type of fixation and how it is performed may affect the risk of non-union fracture (Ferreira et al., 2016a). Plates and screws have been suggested as a better choice for uncomminuted tibia shaft fractures and locked intramedullary nailing for comminuted fractures (Huang et al., 2008). The sources of treatment failure in femoral shaft non-unions treated with intramedullary nailing has been identified as a lack of immediate weight-bearing, infection and open fractures (Shroeder et al., 2009). Following locked intramedullary nailing, favourable results with immediate weight-bearing in comminuted diaphyseal femoral fractures has been reported (Kubiak et al., 2013).

Excessive soft tissue dissection contributes to an increased risk of non-union fracture development (Ferreira et al., 2016a). Non-union fracture in excessive tissue damage is mainly associated with chances of infection, of which early soft tissue coverage to promote proper healing was suggested (Harry et al., 2008). Health risk-related factors are dependent on the multi-disciplinary team to work effectively to reduce the chances of complications occurring during patient hospital stay.

2.6 EFFECT OF DIFFERENT CORMOBIDITIES AND MEDICATION ON FRACTURE NON-UNION

Fracture non-union is happening in different factors and their effects differ in occurrence, although the management and the outcomes may be similar.

2.6.1 Effects of HIV

Low bone mineral density is prevalent in HIV positive patients (McComsey et al., 2010b). The causes of low BMD in people with HIV infection seems to be multifactorial and signifies a multifaceted interaction between the HIV infection, traditional osteoporosis risk factors and the ART (McComsey et al., 2010a). The chronic inflammation and possibly the virus itself affects bone resorption osteoclast activity (McComsey et al., 2010b). Low bone density loss is associated with the use of ART. Any imbalance between bone resorption and bone formation leads to loss of bone density, therefore a greater risk of fracture.

There is an amplified prevalence of tardy healing and non-union in HIV positive patients and evidence for a relationship between HIV infection and reduced fracture healing (Harrison, 2009; Richardson et al., 2008). In a prospective study done on open tibia fractures, three of the seven patients with HIV had non-united fractures at six months (Harrison, 2009). The reported prevalence of reduced fracture healing was 3.34 per 100 patients (Yong et al., 2011). HIV positive patients are prevalent to fragility fractures and osteoporosis (Richardson et al., 2008; Watanabe et al., 2010; Yong et al., 2011). Several authors suggest that patients are more likely to develop osteoporosis whilst on antiretroviral therapy (Chiţu-Tișu et al., 2016; Kruger and Nell, 2017), which in turn increases the incidence of fractures in HIV positive patients. Apart from the directly obstructing cellular function in bone remodelling, HIV infection is known to cause derangement in the levels of those cytokines involved in the fracture healing and appears to impair blood supply of the bone (Richardson et al., 2008). Reduced BMI, suboptimal nutrition, and the effects of ART have been recognized as factors that obscure bone healing in HIV positive patients (Richardson et al., 2008; Arnesen et al., 2003). Remodelling in secondary bone healing is affected by altered rated of bone formation and resorption together with the risks of BMD and fracture risk. Callus formation is very crucial for fracture healing (Richardson et al., 2008). The development of woven bone and a subsequent extended remodelling period occurs. Usually osteoclasts exist in small concentrated masses (Richardson et al., 2008). Remodelling process require attraction of the osteoclasts to areas needing repair and move in to sweep away the damaged bone (Richardson et al., 2008). The authors further clarified that osteoblasts initiate bone formation, laying down new bone and repairing the gaps created by osteoclasts (Shapiro, 2008). At the end of this period, the osteoclasts disappear and the tunnel is invaded by osteoblasts, then new bone begins to develop. Blood vessels supplying the area are very crucial as the deposition of new bone is expected (Shapiro, 2008). The author explained that HIV progression disrupts the relationship between bone formation and reabsorption, and that may lead to low BMD. Due to open fractures, internal fixation is used, however HIV infection complicates open fractures as it raises the infection in the area of wound (Harrison, 2009). Therefore, the immune-compromised patients may be adversely affected by the altered inflammatory response (Harrison, 2009).

2.6.2 Effects on diabetes and hypertension

Diabetes mellitus values from deficits in the making of insulin or deficit insulin resistance coupled with inadequate insulin production (Jiao et al., 2015). Diabetes mellitus is a metabolic ailment related with several complications, which include delayed or non-union of bone healing. It is a metabolic disease that will increase fracture risk, interruptions with bone formation and harms recovery (Jiao et al., 2015). The author similarly cited that diabetes losses osteoblast formation, function, and reduces the number of osteoblasts that are critical to the recovery of bone. The association between fracture recovery and diabetes suggests that insufficient insulin production leads to reduced manufacturing of collagen through osteoblasts (Hernandez et al., 2012a). Type I diabetes is additionally related with decreased BMD (Jiao et al., 2015). There was increased fracture risk of the hip in patients with type I and type II diabetes; bone mineral density was decreased in patients with type I and increased in patients with type II diabetes (Valderrábano and Linares, 2018). Diabetes mellitus affects a couple of phases of fracture healing along with early cell proliferation and late phases ensuing in inferior biomechanical properties (Gebauer et al., 2002b).

Later phases of fracture restoration are additionally affected seeing that mechanical power and stiffness are compromised in a diabetes mellitus fracture (Einhorn and Gerstenfeld, 2015; Marin et al., 2018).

The process of bone recovery is compromised in diabetes through decreased bone turnover, expanded inflammation and decreased vascularisation, which in turn impairs fracture recovery (Martin and Nunan, 2015). Diabetes increases osteoclast formation in a wide variety of conditions, including periodontal disease, fracture restoration and osteoporosis (Jiao et al., 2015). Osteoclast deficiency impairs fracture healing, as they are specialised bone resorption cells (Kolar et al., 2010). The author suggested that the bone resorption ability makes osteoclasts irreplaceable for the chronic physiological procedure of bone remodelling as well as for the restore technique throughout bone recuperation (Kolar et al., 2010).

There is additionally an association between hypertension, BMD and serum osteocalcin. Bone density of hypertensive sufferers is appreciably lower, and antihypertensive pills can additionally have a consequence on calcium metabolism affecting the bones as well resulting to non-union of fractures (Ye et al., 2017).

2.6.3 Non-steroidal anti-inflammatory drugs (NSAID)

Fracture healing process involved inflammation phase as a vital step in which prostaglandin production by COX-2 is involved (Geusens et al., 2013). NSAIDs inhibit cyclooxygenase activity to reduce the synthesis of prostaglandins, which are pro-inflammatory, lipid-signalling molecules (Su and O'Connor, 2013). NSAIDs in acute pain after a fracture, or during the postoperative period after fracture fixation play an important role due to the distinct analgesic potency, anti-inflammatory effects, and lesser side effects compared to opioids. NSAIDs, due to their ability to inhibit the production of prostaglandins, alleviate the intrinsic local inflammatory response, desensitising the peripheral pain receptors (Pountos et al., 2012). The mechanism by which inhibition of COX-2 impairs endochondral ossification during fracture healing remains unknown (Su and O'Connor, 2013). NSAIDs inhibit or delay fracture healing to a greater or lesser degree, depending on the specific drug, its preparation, mode of administration, and the ability to inhibit COX-2 (Cottrell and O’Connor, 2010).

2.6.4 EFFECTS ON NUTRITIONAL STATUS

Risk factors for non-union fractures are fracture dependent and patient dependent (Nandra et al., 2016), nutritional status being the one of patient dependent. With the increasing incidence of non-union fractures, the nutritional state of the patients is precarious to understand. Malnutrition adversely affects early callus conformation (Perumal et al., 2007). Irregular collagen fibers that are found in protein results in delayed healing of the fractures and or possible decrease the strength in the newly formed bone which result in non-union of the fracture. Another study added patients with low vitamin D to develop non-union fractures than those who were using the supplement (Ernst et al., 2018).

2.6.5 EFFECTS ON INFECTION

Non-union infection is one of the reported causes of delayed healing (Mills et al., 2016). Fracture patients with infection may present with a failure to heal rather than systemic signs of infection (Mills et al, 2016). The author suggested that all the non-union fractures must be treated as infectious as infection as no systematic signs are observed (Mills et al., 2016

2.7 CLINICAL PATHWAYS OF NON-UNION FRACTURES

The settlement on the effect of clinical pathways on hospital resources and patient outcomes is still not clear (Kinsman et al., 2010). A clinical pathway is a method for the patient-care management of a well-defined group of patients during a well-defined period. The authors further explained that the goals of the clinical pathways to be specific to the significant and strategic points that the chosen group are founded (De Bleser et al., 2006). Depending on the needs of that particular chosen group, clinical pathways can be a range of particular area wanted to achieve from a smaller scope to a huge scope. The aim of the clinical pathway is standardise the regime for the particular chosen group aiming to improve quality of life and outcomes perspective. Clinical pathways aim to address patient expectations by helping to clear the message between the multidisciplinary team (Panella et al., 2008). The message and emphasis are sent through announcement, directing roles and sequencing the activities of the multidisciplinary care team, patients and their relatives by documenting, monitoring and evaluating variances, and by providing the essential assets and outcomes (De Bleser et al., 2006). Clinical pathways are designed and arranged, healthcare strategies of care contiguous an intervention (Resnick, 2014). As stated, clinical pathways may vary, it might define levels of cost efficacy; outcome variation and aiming to reduce particular to support the evidence based standards (Rotter et al., 2010). To have effective clinical pathways vigorous planning and strictly following the procedures, the outcomes in hospitals may be achieved including decreasing reported or known complications, time spent at hospital, recover expenses through planning, and much more (Kim and Lockhart, 2012).

The inpatient experience and processes of care in orthopaedic surgery was successfully monitored and reliable tool for clinical pathways was planned prior (Schwarzkopf et al., 2016). The aim of clinical pathways has been suggested as to optimise the worth and efficacy of care. It has been suggested that the plans must address preparation prior to admission, within hospital care and after patients are discharged (Duggal et al., 2014). Clinical pathways must meet norms comprising of an organised multidisciplinary plan of care, and the clear network to use to the transformation of procedures or suggestion into local structures (Kinsman et al., 2010). In addition to the norms, the phases in a sequence of treatment or care in a plan, pathway, guideline, protocol or other channels, must also be scrutinised (Kinsman et al., 2010). Finally, criteria-based and the standardised care for an explicit experimental or medical problem, method or episode of healthcare in a specific population are included in the criteria (Kinsman et al., 2010). The pathway provides an evidence-based and comprehensive organised management progress arranged in a process, guideline or protocol, which is escorted by a specific period or criteria-based progression (Kinsman et al., 2010). Clinical pathways are evidence-based, incorporating proven best practice but ideally, can be modified to any given hospital environment and culture.

A clinical pathway is described as optimising the excellence and efficiency of care. Clinical pathways might define levels of budget efficacy, decrease practice and outcome dissimilarity, and support evidenced-based criterions of care (Rotter et al., 2010). Through rigorous planning and following of procedures in clinical pathways, hospitals are able to decrease the incidence of complications and length of stay, improve budget planning, and much more (Duggal et al., 2015). Clinical pathways are a reliable tool that monitors the inpatient experience and processes of care in orthopaedic surgery (Schwarzkopf et al., 2016).

There is a dearth of literature studied in clinical pathways of non-union fractures. Determining whether a bone fracture is healed is one of the most important and fundamental clinical decisions made in orthopaedics (Morshed, 2014). Generating and applying clinical pathways is an operational way to restrict healthcare spending (Resnick, 2014). Non-union patients were more likely to use various types of surgical care, inpatient care and outpatient physical therapy than those without non-union

(Antonova et al., 2013). The delayed healing or non-union is sometimes associated with the infection incurred. Patients who developed infections or hardware-related pain experienced significantly higher costs compared to their corresponding control patients (Avilucea et al., 2014). A study that investigated the incidence of non-union fractures found that patients with healing complications reported worse function, quality of life and return to work rates 12 months' post injury (Ekegren et al., 2016).

The literature gathered showed the need of clinical pathways and stated that it may be done in any type of patient and or community.

2.8 STRATEGIES TO ACCELERATE FRACTURE HEALING

Numerous substitute treatments have been established, including electrical stimulation, extracorporeal shock wave therapy, and low-intensity pulsed ultrasound (LIPUS), to avoid risks of surgery (Dijkman et al., 2009). LIPUS is a form of ultrasound that delivers lower intensity (<3 W/cm^2) than normal ultrasound energy and output in the method of pulsed wave (Dijkman et al., 2009). LIPUS has been found to be effective on fracture healing by improving the amount and strength of bony callus and by some other natural and molecular mechanisms (Dijkman et al., 2009a). The use of LIPUS comprises substitutes to assist callus maturation (Salem and Schmelz, 2014). It has been theorised that the micromechanical strains produced by its pressure waves in biological tissues could result in biochemical events that normalise fracture healing (Marsell and Einhorn, 2011). Several studies showed the benefits of LIPUS stimulation in enhancing bone healing after fresh fractures, in delayed or non-union, in upper and lower limbs and showed a good success rate (Dijkman et al., 2009b; Salem and Schmelz, 2014; Watanabe et al., 2010). Moreover, a number of animal studies established substantial benefits for its use as an adjuvant during distraction osteogenesis (Martinez de Albornoz et al., 2011). However, its clinical application in humans to enhance callus maturation has not been sufficiently studied in patients with comorbidities.

Fracture management comes with complications due to surgical management at times; therefore, non-invasive management especially in patients with comorbidities is of importance.

2.8.1 Use of LIPUS to accelerate fracture healing

The electrical possessions of bone material, principally piezoelectricity, inspired some investigators to advance a technique that would have an outcome on the modification of the bone absorption, if the union did not occur in the anticipated time or even to accelerate this metabolism in recent fractures (Fontes-Pereira et al., 2013). Several studies have demonstrated accelerated fracture healing using LIPUS (Coords et al., 2011; Della Rocca, 2009; Linde et al., 2008; Mundi et al., 2009). LIPUS is a class of ultrasound used as an addition to conservative management for fracture remedial, and has been used clinically in an effort to improve fracture healing by exciting bone growth at the fracture site, leading to a lessened recovery time and quicker return to full function when injury occurred (Barry et al., 2015)

Ultrasound is defined as sound waves with a frequency above 20,000 Hz (20 KHz). Ultrasound waves are high-frequency mechanical energy consisting of compression and rare-faction phases with frequency above 20, 000 Hz (20 KHz) and are inaudible to the human ear (Cameron, 2017). LIPUS, in specific, functions as a possible non-invasive therapeutic toward fracture healing. The waves directed by LIPUS induce micromechanical stress in the fracture site, culminating in the encouragement of various molecular and cellular responses involved in fracture healing (Mundi et al., 2009). Ultrasound with intensities of 0.01 – 3mW/cm^2 and frequencies of 1.5 to 3 MHz is a very common physical modality used in clinical practice as a therapeutic method (Tajali et al., 2012).

LIPUS is a class of ultrasound used as an addition to conservative treatment for fracture healing (Mundi et al., 2009; Barry et al., 2015). It is a form of ultrasound that is conveyed into connective tissues as an acoustic wave (Tajali et al., 2012) and works as a non-invasive therapeutic towards fracture healing (Mundi et al., 2009). LIPUS is the application of ultrasound energy at much lower levels than is the current clinical norm. The waves administered by LIPUS induce micromechanical stress in the fracture site, concluding in the stimulation of various molecular and cellular responses involved in the fracture healing (Mundi et al., 2009). There has been a common development over recent years to use LIPUS therapy because the higher intensities may cause tissue damage (Tajali et al., 2012).

The applied energy is the same, but most importantly, the dose is different. The intensity is much lower, typically two or three times lower than the lowest setting on most regular clinical machines (Harrison et al., 2016). Most common parameters for fracture healing are tabulated in Table 2.1.

Table 2.1: Recommended Parameter settings for LIPUS on fracture healing (Harrison et al., 2016)

Unit	**Quantity**
Intensity	30 mW/cm² (0.03 W/cm²).
Frequency	1.5 MHz
Pulse width	200 μs repeated at 1 kHz
Treatment time	20 min/ daily

The duration of LIPUS treatment on fresh fractures starts within 1-14 days after the fracture. In case of delayed union and non-unions, LIPUS starts when healing could not be determined (Tajali et al., 2012). Follow-up ranged from 16 to 208 weeks and depended largely on the expected healing times of the fracture models (Snyder et al., 2012). Coupling gel is used between the skin and the LIPUS head to transmit the signals (Barry et al., 2015).

LIPUS is effective for surgically managed, fresh, type C comminuted diaphyseal fractures of the lower limbs when there is suitable strength at the fracture site (Kinami et al., 2013b). There was an approximate 30% reduction in the union period for type C fractures in the LIPUS group (Kinami et al., 2013a). The author performed subgroup analyses of the combinations "fracture site/fracture type" and "soft tissue condition/fracture type" because of the marked difference in outcome for type C fractures between the groups and the analyses (Kinami et al., 2013). The results showed significant differences in outcome for femur, tibia, and closed fractures, with the union period being approximately 30% shorter in the LIPUS group for these fracture site combinations. The union times in the LIPUS group were 30–40% shorter than in the control group (Kinami et al., 2013a). LIPUS shortened the femur fracture healing period and endochondral ossification in the process of bone healing, involving in endothelial cell migration and neovascularisation near fracture areas (Katano et al., 2011). <u>Alleviation of pain in patients with tibial stress fractures was</u>

reported but did not coincide with the radiological report of bone healing (Uchiyama et al., 2007) which is measured radiologically with callus formation (Griffin et al, 2014). Uchiyama et al. (2007) suggested careful follow up of these patients following treatment with LIPUS. The alleviation of pain following LIPUS treatment in patients with tibial stress fractures was also not followed improved healing (Griffin et al., 2014). However, the weakness of this study which was done in the United Kingdom (Griffin et al., 2014) was that it was based on acute fractures only. Table 2.2 below summarises the effect of LIPUS on different fracture sites.

Table 2.2: Summary of effects of LIPUS on fracture treatment

Effect	Author
Effect of LIPUS on a stress fracture of the tibia - LIPUS treatment did not shorten the period of bone union - No difference in radiological or functional/ clinical healing properties	(Griffin et al., 2014a, Uchiyama et al., 2007)
Time of bone healing measured radiographically - Time to 3rd cortical bridging	(Griffin et al., 2014a; Tajali et al., 2012)
Effect of LIPUS on delayed fractures on non-union fractures - Minimal evidence that LIPUS decrease delayed/non-union fractures - Promotes healing in delayed/non-union fractures	(Griffin et al., 2014a; Jingushi et al., 2007; Tajali et al., 2012)
Effects of LIPUS on clinical healing - Decrease pain within a reduced timeframe - Decreased time to weight bear - Decrease tenderness - Increase callus formation	(Jingushi et al., 2007; Leung et al., 2004; Lubbert et al., 2008; Tajali et al., 2012)

Clinical fracture healing in smokers	(Cook et al., 2001; Mayr et al., 2000; Nolte et al., 2002)
Increase bone mineral content and activated alkaline phosphatase	(Busse et al., 2002; Leung et al., 2004; Watanabe et al., 2010)

2.9 MEASURING FRACTURE HEALING

Currently there is no standard agreement on when the fracture is healed. A systematic review to identify the definition of bone healing done and clinical and radiographic healing were identified as the main criteria used to measure bone healing (Corrales et al., 2008).

2.9.1 Clinical fracture healing

The suggestion for patients with suspected non-union was that they were always inspected for local signs of infection, such as erythema, drainage, and wound problems (Morshed, 2014). Additionally, for delayed union and non-union, the majority of the respondents reported decreased weight-bearing capacity, and this was taken as a most diagnostic criterion followed by pain in patients with fractures (Morshed, 2014). Another author added that weight-bearing and pain or absence of tenderness should be specifically monitored in fractures of the tibia and femur (Sprague et al., 2019). Weight-bearing position has been revealed to be comparable with fracture stiffness in tibial fractures treated with external fixation (Leow et al., 2016; Morshed, 2014). Another study suggested both structural and biomechanical evaluations to assess fracture repair (Burr and Allen, 2019). The outcome measures that should be obtained to assess structural properties of fracture healing include strength, stiffness, rigidity, and toughness of the healing bone (Morgan et al., 2014). The utmost through technique is the amount of the flexibility of a fracture under a specified external load, which includes the trial of precisely evaluating the deformation of the bone. Biomechanical approaches include the measurement of load share between implant and bone by internal or by external sensors; however, clinical measurement of the suppleness of a fracture under a given peripheral load and load share between implant and bone by sensors are used (Augat et al., 2014). However, clinical measurement of fracture healing is very subjective given the specific and variances in perception of pain (Morshed, 2014).

2.9.2 Radiographic fracture healing

Fracture union is mainly assessed using plain radiographs (Morshed, 2014). Callus formation, cortices bridged and closing of the fracture line or gap are indicators of radiographic healing in the lateral and posterior views (Whiley, 2011). Callus formation is measured by dimension and bone bridging (Whiley, 2011). Identification of the callus can be accomplished by outlining the outer and inner margins of the callus on transverse cross-sectional images disseminated along the length of the callus (Whiley, 2011). Four cortices are evaluated in the lateral and anteroposterior radiographs to evaluate the fracture lines of the tibia using the radiographic union score of the tibia (Cekic et al., 2014). A study in Canada conducted radiographic union score of the hip (RUSH) using the same four cortices as a measure of fracture healing (Bhandari et al., 2013). In another study, it was suggested that cortical bridging was a predictor of reliability four months after tibial shaft fracture healing (Lack et al., 2014).

2.9.3 Hospital length of stay in patients with non-union fractures

Generally, hospital length of stay following fracture repair differs according to the patients' comorbidities. Length of stay for fracture healing complications ranges from 1-109 days for all admissions (Dunlop et al., 2016). A study in Melbourne, reported a median length of stay of at least two days (Ekegren et al., 2016). Another observational study reported that non-union fractures are 97% (95% CI 25.8-366.5) more likely to have a re-operation (Fong et al., 2013). Several times, patients who are waiting for an operation are kept in hospital for treatment of other problems, as infection delays them being operated on (Krell et al., 2014). Another study reported increased length of stay unrelated to the surgical management but to the patient's advanced age and comorbidities (Fjeld et al., 2019). Unfortunately, patients with non-union fractures have several comorbidities that may influence on their extended length of stay in hospital, such as diabetes and HIV (Ekegren et al., 2018; Fernandes et al., 2015).

Non-union fracture length of stay is also accompanied with readmission within a few months or years of discharge. Another study reported the median (IQR) time to readmission of eight months following the original fracture (Ekegren et al., 2018).

2.10 SUMMARY

The incidence and prevalence of fractures worldwide is multifactorial. Low-income countries are reported to have a greater incidence and prevalence due to the use of public transportation and type of work the people are using (Pan et al., 2014). However, incidence and prevalence of fractures of the lower limb also rely on patient demographic and socioeconomic factors. Being male and younger than 40 years has a greater risk of lower limb fractures (Valerio et al., 2010). The latter is related to the males being at more risk for high impact injuries at a younger age. Fractures are more prevalent in females in the lower limb as a result of low impact injuries, and in older females' low bone mineral density contributes to the risk (Uusi-Rasi et al., 2019).

The fracture healing process depends on the impact of fracture during injury. Open fractures lead to more complications, such as infections, and therefore the healing process is delayed (Fernandes et al., 2015). Open fractures often require open reduction internal fixation especially when bone fragments are out of alignment (Dagnino et al., 2016). Surgical management of lower limb fractures may have complications that further delays healing, but these complications are patient and bone specific. Loosening of the pin complication, amongst the others, is one of the surgical management complications (Ferreira and Marais, 2012)

Non-union fracture is a permanent failure of fracture healing (Stewart, 2019) and is not only caused by surgical management of the fracture. Patient-related factors such as smoking make the individual more prone to non-union fractures as the nicotine in the blood delays the closing the fracture gap preventing the fracture union (Pearson et al., 2016). Additionally, comorbidities, such as diabetes and other immune-related diseases, decrease the blood supply and increase the amount of fatty tissues in the callus of the bone, therefore creating higher chances of non-union fractures (Martin and Nunan, 2015).

The current practice for non-union fracture, which includes the entire multidisciplinary team, is not well documented, with no published clinical pathway including intervention from all team members for patients with non-union fractures. Clinical pathways require the multidisciplinary team to provide standardised care and to ensure variance and outcomes in different units (Lawal et al., 2016; Schwarzkopf et al., 2016). Clinical pathways can reduce hospital costs, improve patient outcomes and improve quality assurance (Schwarzkopf et al., 2016). In orthopaedics, collaboration between the orthopaedic surgeon and the rehabilitation team may assist in reducing patient costs as the discharge and two parties can agree on return date. The team can also agree on final healing and discharge.

Low research evidence exists for the use of alternative adjuncts to accelerate fracture healing in physiotherapy. LIPUS has been used to accelerate fracture healing (Schandelmaier et al., 2017) as it is used internationally to promote bone growths by providing low intensity waves (Harrison et al., 2016) (Leighton et al., 2017; Mundi et al., 2009; Poolman et al., 2017)). The studies that have been published include populations with low prevalence of comorbidities, such as diabetes, health risk behaviours like smoking and patients with non-union fractures; no studies included patients with HIV.

Treatment with LIPUS should include daily treatment for 20 days and the equipment kept at the patient’s home for application until the treatment time is complete (Mundi et al., 2009). Leaving the LIPUS in a patient's home however requires a number of LIPUS units to be able to provide a number of patients.

Radiographic outcomes are reported as a measure of fracture healing after LIPUS treatment in most studies since the final healing outcome of a fracture is usually measured radiographically (Eastaugh-Waring et al., 2009; Morshed, 2014). Fracture healing is assessed based on callus formation, four cortices bridged and closing of the fracture gap (Morshed, 2014).

CHAPTER 3: PHASE 1 (PART 1): EXPLORING NON-UNION IN LOWER LIMB FRACTURES IN GAUTENG PROVINCE, SOUTH AFRICA

3.1 INTRODUCTION

Non-union can be described as a complication in the healing process of a fracture where the healing of the bones is delayed or does not consolidate, and an intervention is necessary for healing to occur (Giannotti et al., 2013; Moghaddam et al., 2016). Intervention is done to accelerate the healing process, ensure proper bone alignment, restore mobility, function and maintain limb stability and length (Patel et al., 2013). Non-union may also be defined as a result of a disruption of the natural healing process due to certain factors (Ferreira et al., 2016a). These factors either influence the healing rate of a non-union or increase its occurrence. The prevalence of non-union fractures is a result of various factors due to differences in fracture sites, patient demographics, comorbidities and health status (Pearson et al., 2016; Zura et al., 2016). A holistic approach that includes a wide spectrum of factors is imperative in selecting treatment options for patients with non-union fractures. Bone, soft tissue, patient and environmental factors, all affect the prevalence of lower limb non-union fractures (Calori et al., 2008).

The prevalence of non-union fracture can be attributed to contributing risk factors that can be placed into two categories, which are general and local (Calori et al., 2008). General risk factors include demographic, pre-existing comorbidities and lifestyle factors, whilst local risk factors involve fracture type, exposure, infection and trauma (Calori et al., 2007). The presence of non-union is largely dependent on these contributing risk factors. Selecting the best treatment option for the treatment of the non-union fractures is in itself a factor that also influences healing rate. Intramedullary nailing devices have been identified as one of the risk factors in tibial diaphyseal non-union fractures due to increased possibility of infection from the use of nails (Young et al., 2013; Neumann et al., 2016). In patients with open wounds, the use of external fixation is commonly aimed at managing the affected soft tissue structures. External fixation however exposes the patient to more fracture complications than intramedullary nailing due to pins penetrating the skin and soft tissue, thus further increasing the risk of infection (Pairon et al., 2015).

Some researchers have identified age, gender, smoking, HIV, and diabetes as the main contributing risk factors to non-union fractures (Ali, 2014). Other studies have identified diet and concomitant systematic diseases as significantly contributing to non-union fractures (Ferreira et al., 2016b). Diet is not only a contributor to delayed fracture healing (Calori et al., 2007), but deficiencies in vitamin D have also been linked to high rates of fractures in patients (Ringe, 2012). Malnutrition lowers the body's metabolic reactions necessary to optimise fracture healing (Meesters et al., 2018). Anaemic patients have an increased risk of non-union fractures because of low haemoglobin levels, which reduce the aerobic metabolic reactions, altering the capacity of the body to repair damaged cells (Ferreira et al., 2016b). Literature has found that anaemic patients who also smoked increased their risk of non-union by 100% (Varecka and Wiesner, 2012).

Non-union of lower limb fractures is linked to higher morbidities and often causes patients great physical and mental anguish, loss of mobility and decreased activities of daily living (Zlowodzki et al., 2005). Tibial fractures have been found to be 97 times (95% CI 25.8-366.5) more likely to have a non-union fracture and warrant further surgery (Fong et al., 2013).

Non-union fracture complications become progressively expensive and complex (Tzioupis and Giannoudis, 2007) because they take longer to heal (Zura et al., 2015). This is a major concern in African countries with challenges in providing healthcare to increasing populations (Shipley, 2010). A study from within Africa showed that the economic costs of non-union fractures and the consequent treatment puts direct pressure on the economic viability of the affected households (Ikpeme et al., 2013). Understanding the factors that influence fracture healing is the first step in reducing the financial burden to treatment; limited studies have however been done on the healing of lower limb non-union fractures in Africa and their socio-economic impact.

Low impact fractures related to osteoporosis are more prevalent to the elderly (Zhu et al., 2019). A low energy fracture is defined as a fracture that is caused by a slip or fall from a standing height on an even ground or environment (Diamantopoulos et al, 2012; Zhu et al., 2019). These low impact fractures occur during normal daily activities like getting a chair or getting out of a car (Gillespie et al., 2009). The authors explained factors related to low impact fractures as poor footing on the ground, poor balance and coordination, changes in muscle mass and vision and this is more prevalent in elderly patients (Gillespie et al., 2009). In an epidemiological study in Asia, the prevalence of lower limb fractures was 9.17% (Pan et al., 2014). In a study done in the UK, Kay and Jick (2004) reported that females are 17% higher in lower limb fracture prevalence than males. A study in central Africa found a prevalence of 48% in lower limb fractures (Ngunde et al, 2019). Contrarily, in the UK findings, males between the ages of 20 to 40 years had lower limb fracture prevalence than females (Ngunde et al., 2019). Motor vehicle accident is reported as a major cause of lower limb fracture prevalence worldwide (Liu et al., 2019; Ngunde et al., 2019; Pan et al., 2014).

In conclusion, lower limb fracture prevalence is worldwide and the causes are similar although that of Africa surpasses the worldwide prevalence.

3.2 THE AIM AND OBJECTIVES FOR PHASE ONE (PART 1) OF THE STUDY

The aim of this phase of the study was to explore and determine the prevalence of fracture non-union in patients diagnosed with lower limb fractures at academic hospitals in Gauteng Province, South Africa.

The insight on the prevalence of lower limb non-union fractures will result in the anticipation of the likelihood of non-union occurring.

3.2.1. Research question

What is the prevalence and factors associated with lower limb non-union fractures at academic state hospitals in Gauteng Province in South Africa?

3.2.2 Objectives of this phase of the study

The objectives of the study were to:

- Determine the period prevalence of fracture non-union in patients diagnosed with lower limb fractures, at three academic state hospitals in Gauteng Province between June 2013 and December 2014
- Determine the demographic factors of those patients identified with lower limb non-union fracture at three academic state hospitals in Gauteng Province

- Determine the prevalent fracture site by gender and age
- Determine the site of non-union fracture in those patients identified with lower limb fractures at three academic state hospitals in Gauteng Province.

3.3 METHODOLOGY

3.3.1 Study design

This epidemiology part of the study was done using the STROBE guidelines (Cuschieri, 2019). A record review was done one year prior and six months into the commencement of the study. The use of a record review was appropriate as it allowed low-cost access to a large sample for the purposes of establishing the prevalence of fracture non-union. The data could not be considered out of date and was not affected by time, as data at the time of the patient's admission was relevant to the study. This data collection method required the collection of information that is routinely recorded in the hospitals, which minimises recall bias and reduces the need for intrusion into patients' time. The research design did have disadvantages, as incomplete and missing records did present a threat as well as variation in the records that were available at the different hospitals (Sarkar and Seshadri, 2014).

3.3.2 Study population and sites

Files of patients admitted to the orthopaedic wards in Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Chris Hani Baragwanath Academic Hospital (CHBAH), and Helen Joseph Hospital (HJH), with fractures of the lower limbs, were used in the study. These were files of patients admitted with lower limbs fractures one-year prior the start of the study up to six months into the study.

The hospitals were chosen as they are tertiary hospitals in Johannesburg, Gauteng and admit the majority of the patients with non-union fractures. Additionally, the hospitals are also the referring hospitals from primary and secondary hospitals from within Gauteng, and hospitals from neighbouring provinces. A consecutive patient record recruitment method was used according to the inclusion and exclusion criteria listed below.

Inclusion criteria

All files of the patients admitted to the orthopaedic ward with lower limb fractures at CMAH, CHBAH and HJH.

- All the files dated one year prior to the commencement of the study and six months from the date of starting the study (June 2013 to December 2014)
- Only files of patients 18 years and older

Exclusion criteria

- Patients with multiple fractures (different fracture sites) – to avoid confusion of different management written in a different site of fracture – <u>either managed surgically or conservatively.</u>
- Comminuted fractures because they require multiple fracture management

3.3.3 Research Instrument

3.3.3.1 Data collection sheet

The researcher developed a data collection sheet for the record review (Annexure 1). This allowed for the data on the patients admitted with lower limb fractures to be recorded including the type of fracture to ensure records met the inclusion criteria. <u>For records that met the inclusion criteria, the age and gender of the patient, as well as the anatomical fracture site and the presence of non-union were recorded.</u>

3.3.4 Research Procedure

Once ethical clearance (Annexure 2) had been obtained, permission to access records was sought from hospital management and the orthopaedic department heads. Records were accessed retrospectively between one-year prior to the commencement of the study and six months from the commencement of the study. A pilot study using the above procedure was conducted with the first 10 records of patients. The feasibility of the data collection sheet (Annexure 1) and the quality of information obtained were assessed to ensure that all information required could be obtained.

The patient record book was requested from the orthopaedic ward and the file numbers and names of patients who were aged 18 years and above were documented on the data collection sheet. Information received from the orthopaedic ward was then taken to the record department where the records were searched according to the record number and patient name. The staff working at the records department guided the researcher as to where to find the records, the researcher reported to staff and they assisted or they reported where the file/s were.

3.3.5 Ethical clearance

Ethical clearance for the study was sought and granted from the Human Research Ethics Committee of the University of the Witwatersrand (M130952) (Annexure 2). Furthermore, permission to conduct the study from CHBAH, CMJAH and HJH was requested from the Hospital Chief Executive Officers (CEO), the Heads of Orthopaedic departments and the Heads of Records departments.

3.3.6 Data analysis

The number of patients admitted with lower limb fractures over the 18-months that records were reviewed, was ascertained. The number of patients who were diagnosed with lower limb non-union fractures among this cohort was established, as was the presence of other comorbid conditions such as HIV, diabetes and hypertension. Data were collected and saved in a Microsoft Excel database and thereafter transferred to the Stata database for analysis. Period prevalence was presented in frequencies, proportion and associated 95% confidence intervals, means and frequencies.

3.4 RESULTS

3.4.1 Introduction

Over the period of 18 months, <u>3847</u> patients were admitted in three academic state hospitals presenting with lower limb fractures. The patient ages, whose records were reviewed, ranged from 18 to 108 years with a mean age of 44.69 (SD=18.43) years. Of these patients 2192 (57%) were male with a mean age of 41.5 years and 1650 (43%) were female patients with a mean age of 49 years; 28 patients (0.72%) were reported to have non-union fracture.

3.4.2 Fracture prevalence

3.4.2.1 Gender and anatomical fracture site

Table 3.1 shows the results of the frequency of the fractures and prevalence by gender and anatomical fracture site based on the patients admitted. The results shown in Table 1 reflect that total male prevalence was 58.7 per 1000 patients with a frequency of 58.7% (n=2259), which was higher than the female prevalence of 41.3 per 1000 patients with a frequency of 41.3% (n=1588). There were 671 more male patients with fractures but the difference in prevalence between males and females was not significantly different. The most prevalent fracture site observed was on the femur, with 33.5 per 1000 patients with a frequency of 33.5% (n=1289). Of this number, the majority of patients were male at 18.3% (n=704), while 15.2% (585) were female. The second highest prevalent fracture site was Weber B, with 17.3 per 1000 patients with a frequency of 17.3% (n=667) of the patients. Weber B is a fracture of the fibula at the level of the syndesmosis commonly accompanied by partial rupture of the syndesmosis. A higher frequency for this fracture site was also found in males at 9.54% (n=367) than in females, who made up 7.8% (n=300) of the patients. Fractures of the tibia/fibula were the next most common fractures at 16.1% (n=618), which was higher in males at 10.84% (n=417) than in females at 5.2% (n=201).

Table 3.1: Distribution of fracture by gender and anatomical fracture site

Fracture Site	Male	Female	Total	P-value difference between males and females	Prevalence per 1000 for patients with fractures
	% (n)				
Femur	18.3 (704)	15.2 (585)	33.5 (1289)	0.727	335 per 1000
Tibia	9.05 (348)	5.04 (194)	14.1 (542)	0.422	141 per 1000
Fibula	0.81 (31)	0.68 (26)	1.48 (57)	0.798	148 per 1000

Patella	2.2 (83)	0.83 (32)	2.99 (115)	0.017*	299 per 1000
Tibia/Fibula	10.84 (417)	5.2 (201)	16.1 (618)	0.211	161 per 1000
Talus	0.36 (14)	0.13	0.49 (19)	0.001*	4.9 per 1000
Calcaneus	1.7 (66)	0.49 (19)	2.21 (85)	0.019*	2.21 per 1000
Weber A	2.3 (87)	2.7 (104)	4.96 (191)	0.617	4.96 per 1000
Weber B	9.54 (367)	7.8 (300)	17.3 (667)	0.813	17.3 per 1000
Weber C	2.2 (85)	2.6 (100)	4.8 (185)	0.665	4.8 per 1000
Metatarsals	1.5 (57)	0.57 (22)	2.1 (79)	0.080	2.1 per 1000
Totals	58.7 (2259)	41.3 (1588)	100 (3847)	0.089	

Significance p≤ 0.05* p≤0.01**

The only fractures that were significantly more prevalent in males in this sample were of the patella, talus and calcaneus in the foot. These were the fractures with the lowest prevalence. Although the talus fracture, at the lower part of the ankle joint, had a low total prevalence of 0.49 per 100 patients with a frequency of 0.49% (n=19), it was higher in males at 0.36% (n=14) than in females at 0.3%. The only fracture sites for which females had a higher frequency were for Weber A, which is a fracture of the lateral malleolus distal to the syndesmosis and Weber C, which is a fracture of the fibula proximal to the syndesmosis.

3.4.2.2 Gender and age of patients with fractures

Figure 3.1 represents the period prevalence of fractures by age group and shows the mean age. Fractures were more common in males up to 50 years of age, after which they were more common in females, particularly above 71 years of age (Figure 3.1).

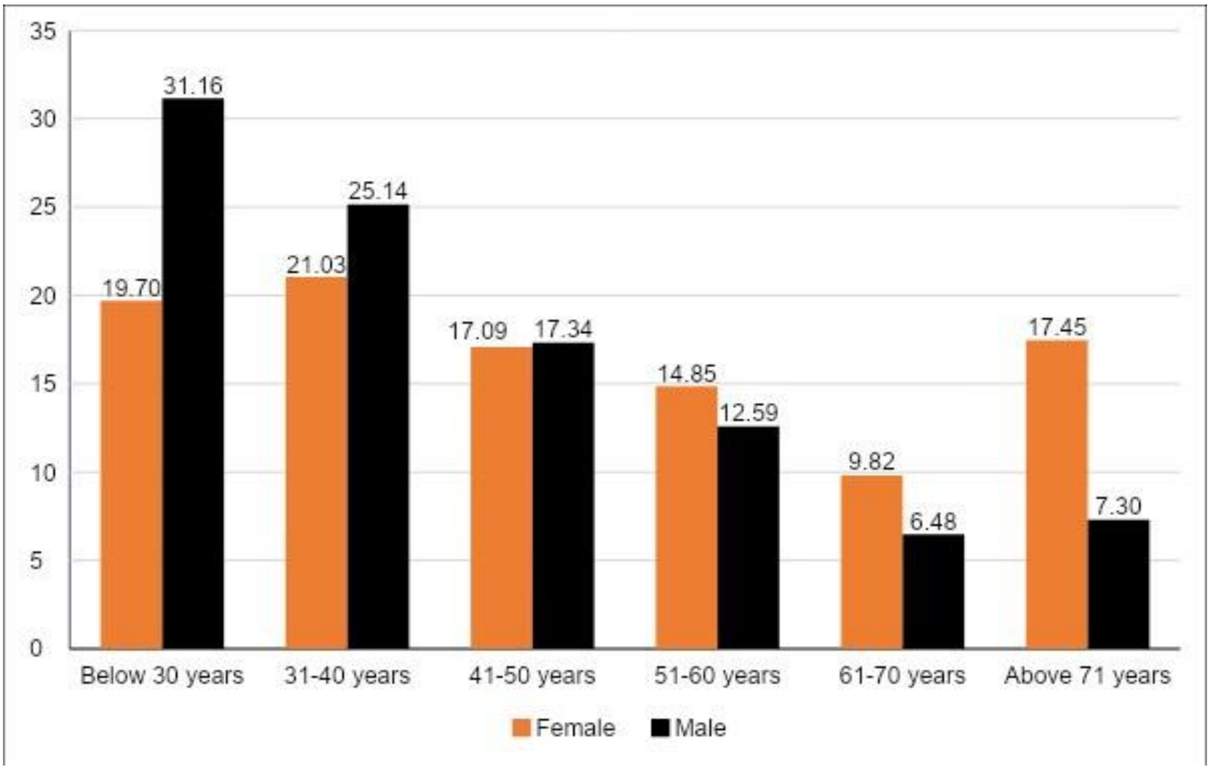

Figure 3.1 Period prevalence of fractures by age group

Figure 3.1 above demonstrates that prevalence of lower limb fractures is more common in patients below 40 years in both genders and mostly higher in males. However, aging in males does not necessarily result in increased fracture prevalence.

3.4.3 Fracture non-unions

3.4.3.1 Gender, anatomical fracture site and age

Table 3.2 shows the results of non-union fracture frequency of the lower limb by fracture type and gender in 28 patients. Prevalence is presented according to the patients with fractures as well as those with non-union fractures.

Table 3.2: Fracture non-union by anatomic fracture site and gender

Non-union fracture site	**Male**	**Female**	**Total**	**Prevalence for patients with non-union fractures (%)**	**Prevalence for patients with fractures (%)**
	% (n)				
Femur	14.3 (4)	21.4 (6)	35.7 (10)	35.7 %	0.82 %
Tibia	14.3 (4)	10.7 (3)	25 (7)	25 %	0,70 %
Metatarsal		3.6 (1)	3.6 (1)	3.6 %	0.02 %
Talus	7.1 (2)		7.1 (2)	7.1%	0.18 %
Patella	7.1 (2)		7.1 (2)	7.1 %	0.18%
Tibia/fibula	7.1 (2)	3.6 (1)	10.7 (3)	10.7%	0.27 %
Fibula		3.6 (1)	3.6 (1)	3.6 %	0.02 %
Weber	3.6 (1)		3.6 (1)	3.6 %	0.02 %
Tibial plateau	3.6 (1)		3.6 (1)	3.6 %	0.02 %
Total	57.1 (16)	43 (12)	100 (28)		

The total period frequency of non-union fractures was higher in males at 57% (n=16) than in females at 43% (n=12). The highest frequency of fracture non-union site was the femur at 35.7% (10), with females having a higher prevalence at 21.4% (n=6) than males at 14.3% (n=4). The total prevalence in the group with non-union fractures was 35.7 per 100 and for the entire sample with fractures of the lower limb 0.82 per 100.

Table 3.3 indicates fracture non-union prevalence in the lower limb by anatomic fracture site and gender with age.

Table 3.3: Fracture non-union by age according to anatomic fracture site and gender

Non-union fracture	Mean (SD) Male ages in years	Mean (SD) Female ages in years
Femur	54.75 (16.86)	47.66 (13.01)
Tibia	27.75 (9.17)	48.66 (17.15)
Metatarsal		57 (0.0)
Talus	45 (1.41)	
Patella	44 (16.97)	
Tibia/fibula	30.5 (2.12)	27 (0.0)
Fibula		59 (0.0)
Weber B	53 (0.0)	
Tibial plateau	43 (0.0)	

Some data in Table 3.3 represents a single participant and therefore there is no variation in the age and no standard deviation that can be provided. The mean age of male patients with non-union fractures of the tibia was younger (27.75; 9.17) than that of females (48.66; 17.15), although mean ages for femur fractures were similar. The age distribution for patients with lower limb non-union fractures ranged from 20 to 72 years. Patients over the age of 45 years had more non-union fractures (28.6; n=8) in the femur. The least common non-union fractures were Weber group, metatarsal and patella. Figure 3.2 represents non-union fractures by age group and shows the mean age.

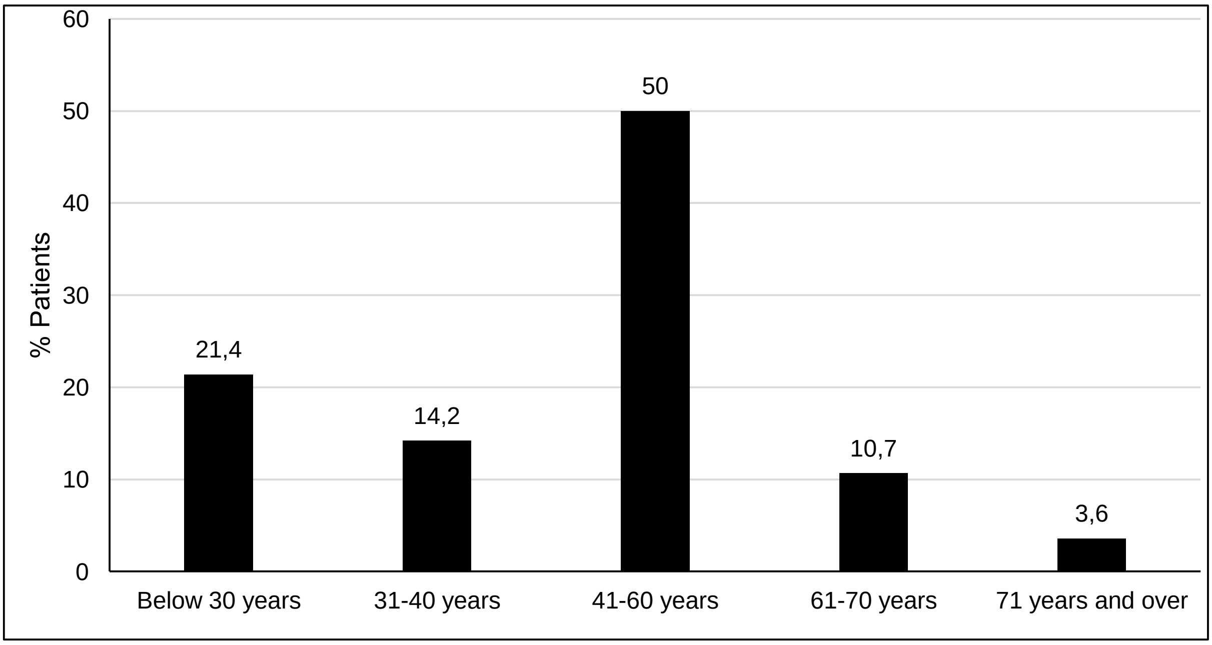

Figure 3.2: Distribution by age group for non-union cases

Non-union fractures were more common in patients who were between 41 and 60 years of age. Patients above 60 years demonstrated minimum prevalence to fracture non-union.

3.5 DISCUSSION

3.5.1 Introduction

Fracture non-union is an understated complication of fracture healing but devastating enough to leave patients with permanent disability. Numerous dynamics account for the causes of non-union fractures in the lower limbs, comprising patient-related and management factors. Patient-related factors include cigarette smoking, which accounts for an increased non-union rate (Pearson et al., 2016; Zura et al., 2016). Many factors increase the propensity of the human body to fractures and worse still, delayed fracture healing or non-union. Some dynamics include the type of transportation used on a daily basis. The infrastructure during activities of daily living may also lead to prevalence of fractures. Numerous confounders are not under control, such as comorbidities that accelerate risks to fracture occurrence, such as osteoporosis. Motor vehicle accidents are also not controlled and may lead to open or closed fractures. Depending on the impact of the injury and type of bone, fractures may be simple, or comminuted which require more diverse management than simple fractures in order to align the bones adequately.

Regrettably, there are certain factors that have an impact on the healing of the fractures that can be controlled and those that cannot. If a fracture is comminuted, intramedullary nailing or external fixation will be used depending if the fracture is closed or any soft tissue structures are affected. The instruments used to align the bone may lead to infection, which in turn, may delay healing or cause non-union fractures. Medical management is not the only cause that may lead to poor healing but lifestyle as well, such as diet. Diet contributes to poor fracture healing but restricted to the availability of the accurate intake, which in turn becomes the challenge. Age and gender cannot be controlled but have an impact on fracture healing. Types of bones vary and so do their healing rate. Lower limbs are weight-bearing bones, which take the whole body weight during activities of daily living. To date in South Africa, the prevalence of lower limb non-union fractures is unknown. The objective of this study was to determine the prevalence of lower limb non-union fractures in three academic state hospitals.

3.5.2 Prevalence of lower limb fractures

Lower limb fractures were divided into categories of different fracture site/type by gender and age. Femoral fractures had the highest prevalence at 33.5% (33.5 per 100 patients) of the total sample with males having a higher prevalence than females. This is in line with an epidemiological study in Tanzania, where males had 33% prevalence in femur fractures (Hollis et al., 2015). A study in France reviewed records in low, middle and high-income countries and reported that males from low to middle-income countries were more likely to have femoral fractures (Matityahu et al., 2013).

In this study, femur fracture was more prevalent in females (35.7%) than in males (14.3%). A recent study conducted in KwaZulu-Natal, South Africa, associated the high prevalence in females as osteoporosis related and also to an increase in age (Dela et al., 2020). However, the study did not find the hip fracture risk factors and the contribution in decrease bone mineral density in osteoporosis patients.

Some researchers have highlighted the link between socio-demographic traits, lifestyles, genes, even environmental climate and fracture prevalence (Asplund and Mezzanotte, 2015; Rodriguez-Merchan et al., 2013). Higher fracture prevalence amongst males may be related to the greater number of outdoor tasks and high impact activities involved, in comparison to females, who are more involved in domestic activities (Jindal et al., 2016). Males have a high propensity to lower limb fractures through high force impact injuries, such as contact sport and motor vehicle accidents, where the fracture pattern becomes significantly more comminuted (Zura et al., 2016). Another study found that most fractures occurred in the tibia/fibula for males, which differs from the current study where the femur was the most common site for in males (de Andrade Rodrigues et al., 2012). Conversely, it must be noted that the latter study did find the femur as the most common fracture site for patients over 50 years of age. The high prevalence of femur fractures in the stated age may be increased due to risks of osteoporosis (Silva et al., 2015). The prevalence in the current study does correspond with a study by Jindal *et al.* (2016) who found that femoral fractures were the most common in all ages. In contrast to these findings, an epidemiological study done in the United States, found females were more likely to have fractures of the lower limbs than were males (Zura et al., 2016). Studies have reported that women have low bone strength (Keyak et al., 2011), and lose bone 10 years earlier and faster compared to male patients (Alswat, 2017).

The prevalence of fractures was found to be higher in males up to the age of 70years in this study and higher for females after 70-years of age. Associations with increasing age, low bone mineral density and smoking were found to be significant risk in fractures in older males (Cauley et al., 2016). A local study reinforced the change in the prevalence of fractures in males when compared to similar fractures in females after the age of 50-years (Cassim et al., 2013) where risk factors for fractures are attributed to low bone mineral density post-menopause (Qaseem et al., 2017). A study in Brazil also supported the high prevalence of femur fractures in females in the older age groups (Oliveira and Borba, 2017) and these findings were reflected in this study where the percentage of females with fractures was only greater than that of males after the age of 50 years. It was clear in the study that the prevalence of fractures was gender related, and fractures occurred more frequently in younger males and older females. Literature indicates the risk factors may differ for younger males who are more frequently exposed to trauma due to work and leisure pursuits before the age of 40 years (Jindal et al., 2016).

3.5.3 Prevalence of lower limb non-union fractures

Non-union fracture prevalence was disseminated among all ages in this study but more commonly in the age group 41 to 60-years. The risks of non-union fractures in this age group is based on patient-related risk factors, such as smoking, and beginning or addition of comorbidities as patients grow older (Hankenson et al., 2014; Hernandez et al., 2012b). The percentage of non-union fractures was lower (0.72%) than that reported in the United States, where 4.9% non-union fractures were found over 24 months (Zura et al., 2016). However, the population in the latter study was dissimilar from the present study, as it looked at all anatomical regions, whereas the current study only looked at the lower limb fractures. Secondly, the study also focused on multiple fractures, while this was an exclusion criterion in the current study. Therefore, the results in the current study may be restricted by the exclusion mentioned above. In our study, 3847 patients with fractures were admitted to the three state hospitals and records were reviewed over 18 months. This figure does not only reflect patients from the 5,635127 who live in the Johannesburg Metro where the hospitals are based, but also patients referred to these hospitals from other provinces, so it was not possible to accurately estimate the size of the population of the patients with fractures represented.

The prevalence of tibia non-union fractures in this study was lower than internationally reported. In a study of tibia shaft fractures, a 12% prevalence of non-union was found amongst 853 patients (Antonova et al., 2013). The low prevalence of tibia fracture non-union may relate to the exclusion of multiple and comminuted fractures from the study, since these fractures have been reported to have a higher incidence of non-union (Zura et al., 2016). In South African tertiary hospitals, patients are often referred to the outlying or district hospitals where they originally came from for follow-up and may not return when fracture non-union is diagnosed. Another explanation for low prevalence in this study could be an exciting proposed new management of tibial non-union treatment algorithm recently introduced in South Africa, which appears to introduce a high union rate. This treatment algorithm included physiotherapy services, such as joint mobilisation, weight-bearing activities and normalising gait pattern in the management (Ferreira et al., 2016a), which is the current practice in hospitals. The tibial treatment algorithm could be beneficial if used in all the anatomical structures of the body to reduce the non-union prevalence globally.

When considering the age of the patients presenting with non-union, half of the patients in the current study fell into the age group of 41-60 years. Mills et al. (2017), who suggested multifactorial causes, support the prevalence of non-union fractures in younger patients up to 50-years of age. The age group 41-60 years consists of the working class, which are susceptible to motor vehicle accidents (MVA) during activities of daily living. Injuries that cause fractures during MVAs are normally severe that they lead to comminuted and multiple fractures, which are some of the risk factors associated with non-union fractures (Mehrpour et al., 2015; Zura et al., 2016). Other risk factors include the patient's comorbidities, as discussed below, as well as surgeon-related factors in relation to the type of fixation used (Mills and Simpson, 2012). Unsatisfactory reduction and reamed nailing of the distal femur was found significant in relation to the non-union fractures (Ma et al., 2016). Surgical intervention may increase the chance of non-union fracture including the type of fixation and how this is executed (Ferreira et al., 2016a).

In addition to the stated risk factors in the age group 41-60 years due to MVA, there are also patient-specific risk-related factors, such as obesity, diabetes and smoking (Zura et al., 2016). Several studies have shown that smoking has influenced delayed or non-union fractures (Patel et al., 2013; Zura et al., 2016). The prevalence of smoking in South Africa is high at 18% of the population however, in the age group 41-60 years the prevalence is slightly less than for younger individuals, and decreases as individuals' age. A prevalence of 24% for those younger than 44 years was reported, 14% for those between 45-54 years and 8% for those older than 55 years (Reddy et al., 2015). Therefore, although smoking may affect fracture healing in this age group, it may have less of an effect than for younger patients.

Similarly, diabetes is perceived as a worldwide epidemic, with a negative impact on blood vessels, which adversely affects the skeletal system, causing detrimental bone effects such as impaired bone healing (Marin et al., 2018). A study in South Africa revealed a 9.2% prevalence rate of self-reported diabetes between the ages of 5160 years (Werfalli et al., 2018), indicating this may be a factor for non-union fractures in this age group in this study.

The gender distribution for non-union fracture followed a trend that was similar to the Scottish population (Mills and Simpson, 2012). Non-union fracture of the femur was more prevalent in females, with more males presenting with tibia non-union fractures (Mills et al., 2017). These findings are supported by Ikpeme et al. (2013), in their study in Nigeria, where the femur was the most common fracture site in which nonunion occurred in 40.4% (n=21) of females. The overall incidence reported by Mills and Simpson. (2012) was in males (57%) compared to females (43%), and this was similar to the study by Zura et al. (2016) on 18 different bones.

This gender distribution was attributed to high impact force activities resulting in open fractures in males, which increases the risk for non-union (Antonova et al., 2013; Zura et al., 2016) due to infection. It is most likely that high impact force injuries may have fractures with an open wound (Elniel and Giannoudis, 2018) and these often develop an infection as a complication. A study investigating the incidence of infection six hours after trauma found an infection rate of 13.24% (Fernandes et al., 2015). An infected wound may require multiple surgical procedures for soft tissue management whilst the actual fracture problem is stagnant. The complication of infection is due to not only the open wound or soft tissues, but may be associated with the surgical management tool used to reduce the fracture. The grade of the open fracture was significantly associated with infection and associated with non-union (Yusof et al., 2013). Fractures with open wounds are often surgically managed with external fixation or intramedullary nailing (Giovannini et al., 2016). External fixation is known to have the complication of hardware failure and pin track infection. A study in New York reported pin track infection in all the patients studied (Chan et al., 2010). A study comparing external fixation and internal fixation reported that patients treated with external fixation were in more agony from the injury and had larger bone defects than patients treated with internal fixation (Wang et al., 2017), however, the gender difference was not distinguished.

3.6 LIMITATIONS OF THE STUDY

Although the study considered a large sample, factors that have an impact on non-union fracture were not considered or collected from the records. In view of the comorbidities, which may affect non-union fracture in South Africa as discussed above, it would be useful, in the future, to include other medical and health risk behaviour in a record review of this type. We excluded multiple fractures in the ipsilateral limb as we anticipated the incidence of getting another fracture may be high if you had a prior fracture (Gehlbach et al., 2012). The exclusion of multiple and comminuted fractures may also have affected the prevalence of non-union fractures reported in this study, and inclusion criteria in future studies need to consider this variable.

3.7 SUMMARY

In conclusion, non-union fractures are more prevalent in males than in females, with femoral fractures prevalent in females and tibial fractures prevalent in males. The cause of the high prevalence of femur and tibia fractures in females and males respectively is yet unknown and therefore it is recommended that further studies should focus on the fundamentals of prevalence on precise anatomical sites. Non-union fractures are prevalent in the age group of 41-60 years; possible reasons may be the activities of daily living that include high impact activities.

CHAPTER 4: PHASE 1 (PART 2): FACTORS INFORMING THE DEVELOPMENT OF A CLINICAL PATHWAY AND QUALITY OF LIFE POST NON-UNION FRACTURES OF THE LOWER LIMB.

4.1 INTRODUCTION

A non-union fracture is a permanent failure of the bone healing process (Ardehali et al., 2018), which then requires another course of treatment to be administered (Giannotti et al., 2013). In clinical practice, both clinicians and patients contemplate non-union fracture as an unfavourable outcome like any other complication. Non-union is difficult to anticipate at the time of injury and during the healing process (Nandra et al., 2016). Non-union fractures of lower limbs in patients may have a magnified negative effect on the physical functionality of the patient because of limited mobility and this is likely to affect their quality of life. Patients' perspectives on the quality of life because of lower limb fracture non-unions have not been well documented, especially in developing countries such as South Africa (Zlowodzki et al., 2005).

Improved surgical techniques and advanced rehabilitation care and change in technology have been introduced in the management of non-union fractures (Nandra et al., 2016). However, despite these advances in care, the clinical pathway that provides clinicians with a guide to the intervention of patients with lower limb non-union fractures is still unclear. The healing process of non-union fractures differs with each anatomical region, pre-existing comorbidities and the fracture type (Ferreira et al., 2014), thus suggesting that clinical pathways may be useful to inform treatment to accommodate these differences.

A quantifiable representation of factors in a clinical pathway related to non-union fractures from start to completion is imperative to guide the healthcare practitioners in planning treatment and the prevention of poor quality of life for the patients. Including the management of poor quality of life is essential in a diverse clinical pathway, if the patient is to be viewed holistically. A multidisciplinary team of healthcare professionals should follow this clinical pathway to provide and manage all possible consequences for these patients as well as to secure their best potential outcome (Bukata et al., 2011). This is in-line with the complex treatment and costs associated with management of non-union fractures (Burgers et al., 2014), as well as the recurring follow-up these patients require to achieve a positive outcome.

4.1.1 Clinical pathways

"A care *(clinical)* pathway is a complex intervention for the mutual decision-making and organisation of care processes for a well-defined group of patients during a well-defined period" (Vanhaecht et al., 2007: p1). Defining characteristics of clinical pathways include:

(1) "an explicit statement of the goals and key elements of care based on the context in which the patients are treated, evidence, best practice, and patients' expectations and their characteristics
(2) the facilitation of the communication among the team members and with patients and families
(3) the coordination of the care process by coordinating the roles and sequencing the activities of the multidisciplinary care team, the patients and their relatives;
(4) the documentation, monitoring, and evaluation of variances and outcomes and the identification of the appropriate resources" (Schrijvers et al., 2012), page 1.

The establishment and development of clinical pathways starts in the selection of an appropriate clinical condition with an identified need in terms of patient and clinical care (Lord et al., 2013). The key selection criteria to develop a clinical pathway includes the collaboration of all the healthcare professionals involved as well as greater patient involvement (Kinsman et al., 2010; Rosstad et al., 2013). Research indicates that clinical pathways are effective in monitoring acute clinical care and lead to better patient outcomes after a period of three months (Schwarzkopf et al., 2016).

The phases in the development of clinical pathway include:

- Screening phase – allows for collection of data on the current care process before the development of the pathway
- Project management phase - put together the core team and the working group
- Diagnostic and objectification phase – critical evaluation of current care and existing evidence

- Development phase
- Implementation phase
- Evaluation phase (Vanhaecht et al., 2007).

The initial phase or phase one in a clinical pathway development is a screening phase used to understand the existing care situation, characteristics of the patients and the results of the treatment that patients receive including the follow up care. This information should indicate if a clinical pathway is needed and the extent of the implementation.

The main aim of this study was to complete aspects of phase one of a clinical pathway development to establish patient and context factors related to fracture non-union to develop standardised clinical care, which would provide effective patient outcomes. Revising and reshaping treatment options for fracture non-union through the implementation of clinical pathways should involve improvement of care by the entire multidisciplinary team (Verdu et al., 2009). The scope of this study was however based on and limited to the physiotherapy clinical practice for non-union fractures. The role of other healthcare practitioners involved in the management of the patient was reviewed in Chapter 2, but they were not involved in the development of the proposed clinical pathway for patients with fracture non-union at this stage.

The development of a proposed clinical pathway for lower limb non-union in this phase of the study aimed to contribute towards positive patient outcomes and optimise resource utilisation in relation to physiotherapy practice; this includes reducing hospital costs and accelerating patient mobility and improving their quality of life (Cheah, 2000). To inform the development of a clinical pathway data was sought on patient demographics, health status and outcomes related to functional impairment after six months (Vanhaecht et al., 2012). Furthermore, patient perspectives were addressed by determining their quality of life to assist in identifying holistic management of these patients.

Clinical pathways are concerned with the standardisation of care processes in the healthcare system based on evidence-based practice for a specific group of patients (Kinsman et al., 2010). Literature revealed that non-union fractures require repetitive surgical management and physiotherapy joint mobilisation post-surgery. This physiotherapy intervention is crucial for full recovery (Ferreira et al., 2016b) and should inform the establishment and development of a proposed physiotherapy clinical pathway that may increase treatment efficiency of lower limb non-union fractures in patients in state hospitals in Gauteng.

Literature supports the use of clinical pathways to create systems that are more efficient by reducing in-hospital complications and errors, improving documentation and promoting patient positive outcomes and safety (Rotter et al., 2010; Schwarzkopf et al., 2016). Hospital complications and errors may be reduced by detecting them early so they can be dealt with before complications arise. To achieve this, voluntary reporting of errors, medical record review, administrative surveillance and clinical observation, based on the clinical pathway guidelines, must be emphasised (Forster et al., 2012). The emphasis on medical record review includes the multidisciplinary team further reviewing identified charts to confirm the identified issue.

Another qualitative study in clinical pathway development suggested that the specificities of a particular context should also be well thought out to secure efficacious clinical pathway development and implementation (De Allegri et al., 2011). Clinical pathways should consider the effects on the budget, quality in care, treatment transparency and how staff are fulfilled with their responsibilities and training involvement (Ronellenfitsch et al., 2008).

The need for clinical pathways has also been identified for lower limb non-union fractures in order to achieve the critical weight-bearing function of the bones of the lower limb that carry the body during mobility, reducing the length of healing. The loss of quality of life due to the inability to participate in activities of daily living that require good balance and joint mobility affected by lower limb non-union fractures (Kim and Lockhart, 2012) must also be considered. The high costs associated with healthcare services for patients with this condition are also of concern (Hipp et al., 2016a), as this may result in healthcare benefits for the patient being limited due to depleted funding (Colkitt, 2016).

There is a paucity of data on the clinical pathways of lower limb non-union fractures. Conversely, the mounting requirement to explore the clinical pathways in non-union fractures is necessary, as there is a rising trend of reduced fracture healing due to numerous comorbidities. To the researcher’s knowledge, no studies have been published that have investigated multidisciplinary clinical pathways of patients with lower limb non-union fractures, internationally and in the African context, despite lower limb fractures being prevalent.

The factors that inform Phase 1 of the development of efficient clinical pathways including outcomes in relation to cost, length of hospital stay and quality of life were considered. The patient and context factors related to interventions used in physiotherapy that could influence these factors were considered to provide guidelines based on evidence that ascertain the most effective functional outcomes and support quality of life of patients with lower limb non-union fractures.

<u>Furthermore, the development of clinical pathways would help in identifying the trails the patients with non-union fractures went through to their final destination, which can impact their quality of life. By finding the information, the use of LIPUS in these patient will be proven if it may make a difference in their clinical pathway, expectantly, it will make a positive change in their quality of life.</u>

4.1.2 Aim of the Study

This study aimed to determine factors that would inform the development of the proposed physiotherapy clinical pathway for patients presenting with non-union lower limb fractures, which included their quality of life and functional outcomes. .

4.1.3 Objectives

- To determine the demographics, health status and current clinical practice including physiotherapy practice-related to patients with lower limb non-union fractures.
- To determine the quality of life of patients with lower limb non-union fractures.
- To determine the functional outcomes of patients with lower limb non-union fractures after a six month follow up period.

4.2 METHODOLOGY

4.2.1 Study design

A prospective quantitative descriptive study design was used to collect data related to the development of the clinical pathway for patients with lower limb non-union fractures. A review of patient socio-demographic and health status, as well as treatment received, from admission to six months' post discharge was completed. The patients' functional status at six months was also established. Information required for clinical pathways included admission date, length of hospital stay, medication given, postoperative complications, mobility status at discharge, return to work or return to previous home status and readmissions within six months (Vanhaecht et al., 2012). A cross-sectional study design was used to determine baseline quality of life data while the patients were still in hospital.

This research design was suited for the collection of both numerical and text data from the patients' records to evaluate current clinical practice, as well as the patients' perspectives required in the development of a clinical pathway.

4.2.2 Population

The study population included patients admitted with lower limb non-union fractures to the orthopaedic department at five state hospitals in Gauteng, South Africa. These patients were managed as inpatients by a multidisciplinary team. All members of the team recorded data on patient management as well as assessments and interventions used in the patients' files. All laboratory and assessment results and administration data, such as date of admission and contact details, access to x-rays and medication prescribed, were all available and extracted from the patients' medical files.

4.2.3 Sample

Patients were recruited prospectively for 11-months (January 2017 to November 2017) and individually followed up for a period of six months. A consecutive sampling method was used to recruit participants with non-union fractures of the lower limbs.

Consecutive sampling is a strict version of convenience sampling where every available patient that meets the inclusion criteria and gives consent is selected, that is, the complete accessible or total population is studied (Martínez-Mesa et al., 2016). Consecutive sampling provides some structure and thus additional rigour in that it includes all patients who are accessible within the defined study period (Straus et al., 2005). By assessing everybody available, a good representation of the overall population is possible in a reasonable period.

Inclusion criteria

Patients were included in the study if they were:

- Diagnosed with non-union fractures of the lower limbs
- Males and females between the ages of 18 and above.

Exclusion criteria were

Patients were excluded from the study if they:

- Did not reside in the Gauteng province, due to difficulties with the follow-up sessions
- Had pathological fractures, and/or multiple fractures.

4.2.3.1 Sample size determination

The sample size was defined as all patients who had a diagnosis of non-union fractures. Total sampling was achieved through consecutive recruitment of all patients were managed for lower limb fractures. On average, two patients with non-union fractures were recruited per month at a five state hospitals in Gauteng. The clinical pathway, analysis of the demographic and health status variables, function and HRQoL were determined using the data from 22 patients with non-union fractures who were recruited.

4.2.4 Description of measuring Instruments

4.2.4.1 Clinical pathway questionnaire

The clinical pathway questionnaire (Annexure 3A) was constructed for this study based on the literature on the composition of clinical pathways, to capture both numerical and text data. The questionnaire comprised two parts:

Part 1: Demographics and health status

The questionnaire was used to collect information on the lower limb non-union fracture X-ray diagnosis date, period of treatment, type of medication and therapy received while hospitalised and the frequency of follow-up post discharge over a period of six months from the time the participants were recruited into the study (Vanhaecht et al., 2012). The clinical pathways questionnaire also collected patient socio-demographic data and information on comorbidities.

Part 2: Outcomes - impairment and functional limitations

The patients' outcome in terms of their functional status (return to work or previous home) at the end of the six months' period was established using the International Classification of Functioning, Disability and Health (ICF) instrument (santé et al., 2001). This process included determining the presence of impairment (decreased muscle strength and range of motion as well as the presence of pain), activity limitations (inability to climb stairs) and participation restrictions (inability to walk for long distances) among the participants.

Content validity of the clinical pathway questionnaire

A pilot study was completed to determine the content validity of the clinical pathway questionnaire. This was established by consulting three experts in the field of orthopaedics together with reading the literature to find consensus. The experts were clinicians who had more than 10 years' experience in orthopaedics and fracture management, and included the Head of the Orthopaedic Unit and Physiotherapy at Steve Biko Academic Hospital, and a physiotherapy lecturer in orthopaedics at the University of Pretoria.

The experts assessed the relevance and clarity of the questions. There was good agreement between the experts achieving a correlation coefficient of 0.72 based on a 4-point scale. This indicated the questions in the clinical pathway questionnaire were all relevant at an acceptable level, as the correlation coefficient was above the recommended cut off of 0.70 (Polit and Beck, 2006).

4.2.4.2. Short Form-36 Questionnaire

The patients' quality of life was determined using the Short Form-36 (SF-36) questionnaire (Annexure 3B), developed by The Boston Health Research Institute in the United States (Ware and Gandek, 1994). It is easy to administer and has become the most widely used quality of life evaluation tool in the world (Zhang et al., 2012).

The SF-36 questionnaire surveys patients' health that is generic and coherent (Ware and Gandek, 1994) and evaluates health status and the quality of life of individual patients. A greater score on the SF-36 indicates better health-related quality of life (HRQoL).

The SF-36 questionnaire includes questions in eight domains that fall under the physical component score (PCS) and the mental component score (MCS). The PCS consists of physical functioning, physical role, body pain and general health, and the MCS consists of mental health, vitality, emotional role and social functioning. The PCS and MCS scores are uncorrelated, which indicates that physical and mental health quality of life may differ significantly in any individual (Farrivar et al., 2007).

Validity and reliability of the SF-36 questionnaire

The SF-36 manual presents criterion validity information on the SF-36 domain scales, comparing scale scores to the ability to work, disease symptoms, utilisation of care, and to a range of criteria for mental health. This supports the use of the SF36 with many diagnoses and in many settings (McDowell, 2006).

The SF-36 has been tested in numerous populations and demonstrated to be reliable (Cronbach's alpha of > 0.90) in most studies (Ali et al., 2005; Linde et al., 2008). The SF-36 has content validity for a range of variables related to health including age, gender, and social class, limiting illness, and outpatient and inpatient status (Burholt and Nash, 2011).

The measure also demonstrates construct validity and is a useful tool for comparing the health-related quality of life and estimating the relative burden of different diseases in several population sub-groups. The outcome measure is sensitive to variations in health state and should therefore be responsive to changes in health (Jenkinson et al., 1993). The SF-36 has been translated into a number of languages and has previously been used in South African (Kastien-Hilka et al., 2017) and African research studies (Frempong-Ainguah and Hill, 2014).

Dattani et al. (2013) evaluated the convergent validity of the SF-36 in lower limb fractures. There was very good correlation between the SF-36 and the Western Ontario McMaster Osteoarthritis (WOMAC) and the Short Musculoskeletal Function Assessment (SMFA) questionnaires. The standard response means for the SF-36 were statistically higher, as was the minimal clinically important difference on which it was based. The SF-36 was indicated as the questionnaire of choice in assessing patients with lower limb fractures (Jansen et al., 2010). The questionnaire has also been used and found to be valid for other orthopaedic conditions, such as back pain (Nemeth, 2006).

4.2.5 Research Procedure

Ethical clearance (numbers M130952; 349/2017; Annexure 2 and 6) and permission from relevant authorities was obtained for the study. The researcher reviewed the admission register at each hospital and all the patients with lower limb non-union fractures in the orthopaedic wards were approached for recruitment to participate in the study. The objectives of the study were explained to the potential participants and they received an information sheet and provided signed informed consent preceding recruitment into the study (Annexure 4A and 4B). Baseline assessment started at the hospital where data for each patient and their care plan were collected from the records. Data collection also included the structured intervention of the multidisciplinary team (Kinsman et al., 2010).

Records were accessed on admission, and daily to identify any newly added treatment and/or therapy given. Other information was obtained from participant interviews, as some of the hospital records were incomplete or in cases where the patient was not diagnosed with a non-union fracture at the hospital where the research was conducted.

Once participants were recruited, they were requested to complete the SF-36 questionnaire in the presence of the researcher immediately after admission. The research assistant helped to identify new patient admissions and started with baseline data, then informed the researcher for follow-up purposes. The researcher continued with home visits while the research assistant, who was also a qualified physiotherapist, continued with the recruitment and treating of some of the participants who were still in hospital. Utilising patient records, participant interviews and through follow-ups, the clinical pathways questionnaire was completed with the participants over six months.

Participants were initially treated in hospital by the hospital physiotherapy clinicians and then followed-up as outpatients. Each participant was followed-up at all outpatient appointments at the hospital, and their progress monitored in terms of their treatment and any changes in recovery noted.

After discharge, the participants were followed-up at the Orthopaedic clinic every six weeks and every two weeks with a physiotherapist in the hospital. All the visits with either doctors or therapists were monitored and recorded. Telephone calls were also used as a method of follow-up between the hospital outpatient appointments that varied from weekly to monthly as some patients had more appointments than had others. Six months after the initiation of the data collection, participants were also followed up at their homes to assess their level of impairment or functional outcomes using the clinical pathways questionnaire based on the ICF (santé et al., 2001). The researcher completed the ICF in the patient's home environment.

4.2.6 Data analysis

Collected data were analysed using Stata version 14. Data from the clinical pathways questionnaire Part 1 and Part 2 and the ICF functional outcomes were presented in frequencies and percentages. Data from the SF-36 were analysed using raw scores and standard scores according to the parameters set down by the test instructions. Text data were also analysed using frequencies.

4.2.7 Ethical clearance

Ethical clearance was sought and received from the Human Resource Ethics Committee at the University of the Witwatersrand (M130952) (Annexure 2) and University of Pretoria (349/2017) (Annexure 6) before the commencement of the study. Permission to conduct the study was also granted by the respective hospitals (Annexure 7 and 8). The patients' informed consent was respected in that they were informed about the purpose of the study and the extent of their involvement by providing a verbal explanation and an information sheet explaining the study (Annexure 4A). Those who agreed to participate in the study gave signed informed consent preceding the commencement of the study (Annexure 4B). The patients were also assured that all the information obtained would remain confidential and anonymous by using codes on all records. The participants were informed of the right to refuse to participate or withdraw from the study at any time and that their withdrawal would not have any effect on their current treatment in the hospital or on discharge. Beneficence was ensured as none of the procedures in this study placed the patients at risk.

4.3 RESULTS

4.3.1 Introduction

Data for the factors informing the development of the clinical pathways were collected from 22 participants with lower limb non-union fractures, in five state hospitals in Gauteng, South Africa. Each patient completed the SF-36 questionnaire and followed up prospectively for a period of six months.

4.3.2 Demographics

The majority of the patients were males (n= 90.9%), single (n= 55%) and below the age of 60 years (Table 4.1).

Table 4.1. Socio-demographic characteristics of patients (n=22).

Characteristics	**Category**	**n (%)**
Gender	Male	20(90.9)
	Female	2(9.09)
Age	20-29	6(27.27)
	30-39	5(22.72)
	40-49	5(22.72)
	50-59	5(22.72)
	> 60	1(4.54)
Marital Status	Single	12(54.54)
	Married	7(31.81)
	Divorced	2(9.09)
	Widowed	1(4.54)
Type of house	Standard	14(63.63)
	Flat	4(18.18)
	Shack	4(18.18)
Currently Employed	Yes	3(13.63)
	No	15(68.18)
	Student	3(13.63)
	Pensioner	1(4.54)

*Standard house - is a brick house with two or more bedrooms, a kitchen and a bathroom.
*A shack – is an unstructured small building from pieces of wood, metals or other materials, often with no water and bathroom services inside.

Other socio-demographic characteristics of this group were that 15 (68%) were unemployed, while four (18 %) lived in informal housing or shacks.

4.3.3 HEALTH STATUS

Table 4.2 outlines the health status of the participants, including the site of non-union fractures in lower limbs, which occurred most frequently in the distal femur and the tibia in 23% of the participants.

Table 4.2. Health status of patients with lower limb non-union fractures (n=22).

Variables		**n (%)**
Diagnosis		
Distal femur		5 (22.7)
Distal tibia		5 (22.7)
Distal tibia/Fibula		1 (4.6)
Medial malleoli		3 (13.6)
Mid-shaft tibia		4 (18.2)
Proximal tibia		3 (13.6)
Proximal tibia/fibula		1 (4.6)
Comorbidities		
Diabetic	Yes	3 (13.3)
	No	19 (86.4)
HIV	Yes	9 (40.9)
	No	13 (59.1)
Health Risk Behaviour		
Smoking	Yes	22 (100)
	No	0 (0.00)
Re-admission within six months due to non-union fracture		
Yes readmission		12 (54.6)
No readmission		10 (45.4)
Duration of non-union fracture		
Less than a year		2 (9.1)
More than a year		16 (72.72)
More than 2 years		4 (18.18)
Hospital related variables		
		Median (Lower and upper quartile)
Length of hospital stay - months		4 (3-5)
Follow-up frequency		6 (6-6)

Patients diagnosed with distal femur and tibia non-union fractures were most prevalent at 22.7% (n=5); Patients diagnosed with mid-shaft tibia non-union fracture followed closely (n=4; 18.6%). The least number of patients were diagnosed with proximal tibia/fibula and distal tibia/fibula fractures, which were only one (4.6%) for each respectively. Comorbidities included diabetes in more than 13% of participants and HIV in 41% of participants. Most of the participants were involved in risky health behaviour of smoking and over half (55%) of participants were readmitted to the hospital within a period of six months due to the complications of non-union fractures. The median length of stay was four months (IQR=3-5), with three participants being admitted for more than 20 months. Participants attended a median of six outpatient follow-up visits (IQR=6-6). Over 70% had non-union for more than one year.

4.3.4 Treatment received

Table 4.3 illustrates the treatment received by the participants with a number of different medications prescribed. Participants received between one and four different pain medications and between one and three different antibiotics over a period of six months for 20 patients with infected fracture sites. The non-union fracture was managed with traction in 45% of participants, with 95% having an external fixation. The majority of these participants had open reduction internal fixation (ORIF) (86%) and all required crutches (90%) or a wheelchair (9%) for mobility. All of the participants had vacuum drainage of their fractures.

Table 4.3. Treatment received by patients with lower limb non-union fractures (n=22).

Variables		**n (%)**			
Medication related to fracture					
Number of different medications		1	2	3	4
Pain medication		9 (40.90)	6 (27.27)	4 (18.18)	3 (13.64)
Antibiotics		7 (31.81)	11 (50.00)	2 (9.09)	
Anti-inflammatories		2 (9.09)			
Fracture management					
Traction	Yes	10 (45.45)			
	No	12 (54.55)			
External fixation	Yes	21 (95.45)			
	No	1 (4.55)			
ORIF	Yes	19 (86.36)			
	No	3 (13.64)			
Negative pressure Vacuum Drain	Yes	22 (100)			
	No	0 (0.00)			
Rehabilitation and other therapy					
Physiotherapy		22 (100.00)			
Occupational Therapy		5 (22.72)			
Dietician		5 (22.72)			
Assistive devices					
Crutches		20 (90.91)			
Wheelchair		2 (9.09)			
Outcome of fracture					
Healed		0 (0.00)			
Amputated		3 (13.64)			
Non-union		19 (86.37)			

Twenty-three percent received occupational therapy and consulted a dietician. The outcome of the fractures after six months was that 14% (n=3) of the participants had an amputation of the limb, while 68% still presented with fracture non-union. The clinical decision for amputation was made in consultation with the patient and the criterion of more than two years of not healing with complications of infection was used.

All participants received physiotherapy treatment and negative pressure vacuum dressings for wound closure. Examples of techniques used for patients with lower limb fractures and associated principles are outlined in Table 4.4.

Table 4.4: Principles of physiotherapy treatment

Examples of techniques used	**Principles of Physiotherapy Treatment**
Deep breathing exercises Percussion and vibrations	Maintain respiratory function post operatively
Gentle soft tissue mobilisation on the affected joint, use of cryotherapy or thermotherapy, active range of motion as tolerated and other electrotherapy equipment	Pain Management
Active/ active assisted or passive range of motion exercises	Joint mobilisation of the affected joint, and joint above and below
Facilitated, free active and active resisted exercise	Strengthening of muscles
Turning, moving up and down and sideways in bed, bridging, push-ups	Promote function in bed
Static and dynamic sitting and standing balance	Re-educate balance
Gait re-education with walking aids and/ or stair climbing	Promote mobility out of bed

4.3.5 Functional Status six months' post non-union

Table 4.5. indicates that all the participants with lower limb non-union fractures who were assessed, presented with impairments. All the participants had impairments in muscle strength and range of motion, activity limitations in stair climbing and participation restrictions as they could not walk for any distance at the six month follow up; this was irrespective of whether they still had non-union or an amputation had been performed.

Table 4.5 Participants functional status according to the ICF after six months (non-union, amputation) (n=22)

International Classification of Function	n(%)
Impairment	22(100)
Activity limitations	22(100)
Participation restrictions	22(100)

4.3.6 Quality of Life

Data from the eight domains of the SF-36 were analysed together with non-union fracture diagnosis as well as the combined scores for physical and mental function. Some standard scores (mean 100: ±15) were well below the functional score cut off of 85, which indicates at risk for impairment in quality of life. Participants scored below 70 (-2SD), indicating dysfunction in the domains of physical function, role limited by physical and body pain, indicating dysfunctional quality of life related to these aspects (Table 4.6).

Table 4.6 Mean scores for the Short SF 36 (n=22)

Variable	Mean	SD	Standard scores SF-36
Physical Function	27.95	21.91	60
Role-limited by physical pain	21.59	17.75	59
Body Pain	26.77	15.30	69
General Health	38.59	21.99	73
Vitality	31.13	11.64	73
Social Functioning	50.00	19.28	72
Role limited by Emotional problems	31.81	29.95	40
Mental Health	38.90	20.91	51
Physical component scores (PCS)	31.11	5.88	72
Mental component score (MCS)	20.61	11.90	56

Mental health and roles limited by emotional problems were the domains that most affected quality of life in these participants. This was confirmed by the mental component score (MCS), which was lower than the physical health component score (PCS). The standard deviations indicated a large variation in the quality of life scores in the sample for all eight domains (Table 4.6).

4.3.7 Summary

This study found that factors that needed to be considered when developing a clinical pathway from the context or situational analysis of patients with lower limb non-union fractures were gender (most patients were male), marital status (being single) and employment status (being unemployed). All patients in this study were smokers with 40.9% of them being HIV positive. Over half of the patients were re-admitted within six months of being discharged due to non-union fractures. The lower and upper quartiles for the hospital length of stay of patients with lower limb fracture patients was three to five months and the main fracture management type was external fixation for 95% of the patients.

Long hospitalisation and access to therapy, particularly physiotherapy for joint mobilisation, maintaining muscle strength and mobility, as well as surgery and prolonged treatment for infection added to the cost of treatment. The supply of assistive devices was included in this cost, as was the cost to the patient in accessing care as an outpatient.

The results of the SF-36 data analysis revealed that lower limb fractures affected both physical mental and emotional health of the participants in relation to quality of life. Social functioning had the highest mean score of 54 in all eight domains, while physical functioning, body pain and role limited by physical factors affected quality of life in the most for these participants~~.~~

4.4 DISCUSSION

4.4.1 Introduction

This discussion will consider the demographics of the study participants, and their health status and the treatment received to recommend a proposed physiotherapy clinical pathway for non-union fractures. The information of the demographic and medical data collected to inform the development of a clinical pathway will be discussed. Lastly, the functional outcomes and quality of life of patients during six months of follow-up will be discussed to accommodate the holistic treatment of patients with non-union fracture when developing the clinical pathway.

4.4.2 Variables considered for the development of a clinical pathway

In developing a clinical pathway, the demographic and medical data about the patients with a specific diagnosis within the context where the clinical pathway will be used needs to be collected so that the clinical pathway can be based on a situational analysis of these variables (Cheah, 2000). Data on demographic and medical variables, which were considered in developing a proposed clinical pathway for non-union of lower limb fractures in this study, were collected in five public hospitals in Gauteng by reviewing patients’ records, interviewing participants and determining their quality of life while hospitalised and following them over six months to determine functional outcomes. As in the study by Sánchez-Hernández et al. (2016), who used electronic medical records to gather initial information, this study gathered data on the patient's demographics and health status. In addition, fracture outcomes after six months were established. Since this phase collected data on factors related to the first step in the development of a clinical pathway (Kinsman et al., 2010), and in this case focusing on physiotherapy, there is a need to expand on the data in order to have a complete and well informed clinical pathway. To complete all the steps required in developing a clinical pathway other comprehensive steps that include a systematic review of all treatment provided by the multidisciplinary team are needed (Van Herck et al., 2004; Vanhaecht et al., 2007). This phase is beyond the scope of this study. Additionally, a retrospective cohort study to compare clinical outcomes before and after implementation of clinical pathways would need to be completed (Lau et al., 2015; Badia et al., 2017). The paucity of data in terms of patients' demographics, health status and functional outcomes in fractures with non-union and characteristics thereof in South Africa was addressed first.

The first phase for the development of a clinical pathway had a wide scope including aspects of the integrated hospital services, patient socio-demographic characteristics and quality of life. It was vital for this study to include a holistic scope for the clinical pathway development as many factors affect lower limb fracture healing. This concurs with another study where shortcomings in practical patient treatment and a holistic view of the patient were highlighted as a gap in clinical pathways (Li et al., 2014). A multidisciplinary approach was considered in this clinical pathway by determining the team members who treated the patients. The results of this study showed a high prevalence of health behaviours and comorbidities in patients, which have been associated with lower limb non-union fractures, and may account for the lack of healing seen over six months, which further affected quality of life, in the current study. This confirms that a multidisciplinary approach still needs to be investigated to comprehensively assess and intervene for these patients using a clinical pathway.

The aforementioned scope needed to be identified so that a profile and care of patients and their outcomes could be presented in future to a multidisciplinary team. This agrees with Cheah (2000), who stated that collaborative efforts of the team to be used to confirm the clinical pathway. To obtain a complete picture that will contribute to a well-informed clinical pathway one needs to establish the role and scope of practice of the multidisciplinary team. The collaboration of multidisciplinary team members in the current study was derived from the record review of the patients, taking into account the following clinical pathway development

- Identify patient population that will benefit from clinical pathway (Hipp et al., 2016b) – in this study lower limb non-union fractures were identified. Clinical pathways are implements to direct the evidence of healthcare to that particular outcome needed (Kinsman et al., 2010).
- Evaluate current practices usually applied from admission to discharge (Burgers et al., 2014; Panella et al., 2003).

  In this study, records were reviewed to gather the information of patient care with non-union fractures from admission to discharge. Patients were followed up for six months' period.

- Create the pathway, by presenting the findings to the interdisciplinary core team of representatives of the professional groups, to consider the length of stay and identify key practices that need to be included in the pathway (Dy et al., 2003). In this study, the findings were not presented to the interdisciplinary team, as the aim was to determine the factors needed to develop the clinical pathway.

The demographic, health status, functional outcome and quality of life results for the participants in this study are discussed below and included in a partial clinical pathway that included physiotherapy for consideration by a multidisciplinary team. The fourth step of developing a clinical pathway, which requires determining research evidence for physiotherapy of lower limb non-union fracture, was also not formally considered in this study as suggested by Cheah (2000).

Extent of non-union fractures in study cohort

Only files of patients where non-union fracture was diagnosed were reviewed, and other patients with fractures in the wards were not considered. The diagnosis of non-union fractures was done due to subjective reports of persistent pain on the fracture site. The subjective evaluation was confirmed by findings of a fracture gap, poor cortices bridged or no callus formed on X-rays.

Patients in this study had a median hospital stay of four months, which is longer than that reported for patients with infected lower limb non-union fractures in other studies (Fernandes et al., 2015). No information was available for South Africa, but in Britain and the USA the mean length of hospital stay is reported as approximately two and a half months (Fernandes et al., 2015; Ikpeme et al., 2013). Although these studies do not mention the use of a clinical pathway for non-union fractures, the implementation of a clinical pathway for open fractures of the lower limb have shown a significant reduction in length of hospital stay from a median 15 to 8 days with total surgeries decreasing by 50% (Tan and Kwek, 2020).

A clinical pathway for the South African context should consider both treatment regimens being used and their effect on reducing hospital stays. Additionally, the impact of demographics and comorbidities found in this group of patients should also be observed if it is related to hospital costs, when developing the clinical pathways.

4.4.2.1 Demographic characteristics of the patient population

The profile of the sample showed that over 90% of the participants in this study were males, which makes it difficult to compare gender differences. However, the fact that there were high percentages of participants who were male reveals a susceptibility of males to non-union fractures in the South African context. To some extent, this is unsurprising as there is a higher prevalence of fractures in general among men than women (Singer et al., 1998). This may highlight the level of physical activity that is higher in men than in women and result in more severe or multiple fractures (Jindal et al., 2016). The findings of the current study agree to some extent to those of another study, which also reported a higher number of males (57%) compared to females (43%) having non-union fractures (Mills et al., 2017).

The average age of participants with fracture non-union in this study was 40.68 (±13.74) years. The results show a similar number of participants in each of the 10year age bands between 20 years and 59 years, with only one participant over the age of 60 years presenting with non-union fracture in this study group. This suggests that the non-union fractures of the lower limbs are more prevalent below the age of 60 years in this context; Mills et al. (2017) report similar results. Non-union of fractures in advancing age reduces callus vascularisation during fracture healing, likely decreasing oxygen levels at the fracture site and countering the exchange of other nutrients that are imperative for healing (Lu et al., 2008).

All the participants except three were unemployed or dependent on a social grant, with one participant being a student. The participants, therefore, came from a low socioeconomic bracket, which meant they were reliant on the under-resourced state healthcare system in South Africa. Although these participants were able to access hospital care in Gauteng Province, which has been found to have a better-resourced public healthcare (Coovadia et al., 2009) compared to other provinces in the country, challenges existed in terms of the length of treatment and outcomes. These may be related to the poor quality of care reported in the public healthcare system and be influenced by adverse events, poor hygiene and poor infection control measures and shortage of resources in the medicine and equipment (Maphumulo and Bhengu, 2019). It is important for the clinical pathway development to consider all these factors to achieve the most effective and cost-efficient care within the context of healthcare availability.

The patients' comorbidities and health risk behaviour also need to be considered as these factors affect treatment outcomes and need to be reviewed in the clinical development. When considering health risk behaviours, all the participants were smokers in this study. Smoking has been found to be significantly associated with non-union in both closed and open fractures of the femur and tibia (Hernigou and Schuind, 2013).

This finding is supported by literature, which indicates that smoking has a negative impact on fracture healing. Castillo et al. (2005) found that patients who currently smoked (37%) and those who previously smoked (32%) had open tibia fractures that resulted in non-union when compared to non-smokers. Current smokers were 50% likely to develop an infection in open tibia fractures (Castillo et al., 2005). Nicotine in cigarettes causes vasoconstriction and predisposes the wound infection, especially in open fractures (Hernigou and Schuind, 2013). Infection causes poor adherence of the jointure, thus leads to non-union fracture (Chaudhary, 2017). It is clear from the available evidence that smoking negatively affects healing of tibia fractures (Patel et al., 2013).

Cigarettes constitute mainly nicotine, tar, nitric oxides and carbon monoxide, which damage healthy tissue and negatively influence fracture healing (Bender et al., 2014). Nicotine from cigarettes has a direct toxic impact on osteoblasts and osteoclasts and indirect influence on Vitamin D, blood vessels, oxygen supply, and mineral content, all of which are vital for maintaining strong healthy bones (Abate et al., 2013). Nicotine inhibits vascular ingrowth and early revascularisation of the bone and diminishes osteoblast function (Pearson et al., 2016). Patients who stop smoking after a fracture injury are not guaranteed accelerated healing due to the lasting effects of smoking in the body (Abate et al., 2013; Ferreira et al., 2016a; Beyth et al., 2015). Non-union was the most common fracture healing complication in comparison to other fracture healing complications in smokers (Hernandez et al., 2012a). This is in line with various other studies that found that smoking decreases the oxygen available to the cells and blood vessels flowing to the fracture site and increased high fracture incidence are the negative effects of smoking (Abate et al., 2013). Smokers have an increased risk of delayed fracture healing, wound complications and delayed fracture union or non-union (Lee et al., 2013).

When considering comorbidities, a high percentage of participants in this study were HIV positive (41%), and 13% had diabetes. Literature suggests that these comorbidities have an influence on the non-union. HIV disease has been linked to bone loss in the past (Mayer et al., 2006). Individuals who are HIV positive have the higher risk of fractures compared to those who are HIV negative, and experience between 30–70% more incidences of fractures due to low bone mineral density (BMD) (Sharp, 2011), and prevalence of osteoporosis is three times higher in those patients taking HAART (Kruger and Nell, 2017). A study by Li et al. (2014), found that HIV male patients between the ages of 19 and 60 had a higher prevalence of fracture healing complications. Nieuwoudt et al. (2020) have confirmed this in their systematic review of studies in Africa and the USA, which revealed that for HIV positive patients with open fractures and who are HAART naïve, the risk for fracture infection is 5.6 times higher than for HIV negative and HIV positive patients who receive HAART and it affects fracture union. A clinical study that analysed surgical treatment in HIV positive patients found the non-union rate in HIV positive patients with fractures to be 5.6% compared to 2% in HIV negative patients (Xu et al., 2017). This finding is very relevant to the context of this study as South Africa has one of the highest HIV infection rates in the world, with 7.7 million infected individuals in 2019 (UNIAIDS, 2020), and this appears to affect the outcome of non-union of their fractures.

In this study, 13.3% of the participants with non-union fracture were diabetic. This comorbidity has been linked with fracture non-union in several studies, which indicates fracture non-union and healing complications (Hernandez et al., 2012a) occur especially if there is poor glycaemic control (Beam et al., 2002). Another study demonstrated that patients with diabetes delayed healing by 87%, thus risking non-union fractures (Jiao et al., 2015). The effect of this comorbidity on fracture healing is a concern in South Africa, as for developing countries, as diabetes prevalence is likely to increase by 69% by 2030 (Shaw et al., 2010).

4.4.2.3 Functional Outcomes

The follow-up from hospital to home included the observation of impairment, activity and participation in the participants' activities of daily living. Patient's outcomes were also observed if they returned to work following lower limb fracture non-union. In this study, all of the participants had poor functional outcomes. These results are in contrast to the study that sought functional outcomes after open extremity fractures done in the United Kingdom, where all the patients identified with non-union fractures at the start of the study were discharged with full fracture union (Ardehali et al., 2018). Another study looked at health outcomes of delayed unions and non-unions of femoral and tibial shaft fractures and found 72% of patients returned to work after a year. It was interesting to note that 54% of them continued to have pain (Tay et al., 2014). Similar to the current study, pain was the second most reported with low mean score in most fracture sites, indicating severe limited functional outcome, and third reported was tibia/fibula fractures with lowest mean value of 17.66 (21.07). No studies were found where ICF in non-union fractures' clinical pathways implementation and development were used. The implementation of clinical pathways should consider impairment outcomes in lower limb non-union fractures because of different anatomical fracture sites in relation to activities of daily living and socio-demographic characteristics, which reduces the quality of life.

4.4.2.4. Quality of life

It was found that lower limb fracture non-unions were related to escalated morbidity, resulting in patient physical, mental and emotional functioning. The results show that physical functioning, role limited by physical as well as body pain, and the role limited by emotional and mental health in patients in the current study were dysfunctional, with standard scores below 70 and scores below 40 for participants with non-union fractures of the lower limbs. This indicated that intervention for quality of life issues that may not have been provided for should be considered as part of the intervention for these patients. In a prospective study involving 215 trauma patients in Canada, 22% of the patients were found to have reduced quality of life based on the criteria for the mental component, reported that they were in process of taking legal action due to a lack of support and intervention for this component (Bhandari et al., 2008).

The vitality function and mental health components also scored well below the norm and this reflects that the patients were still functioning physically, but due to the non-union fracture, mental health was affecting more on their quality of life. Zlowodzki et al. (2005), who found that quality of life was significantly impacted in patients with fracture non-union, support these findings. Contrary to the current study, they found that physical functioning has a more significant impact on quality of life than mental health in patients with non-union fractures (Zlowodzki et al., 2005).

This finding could be accounted for by the properties of the SF-36, which have been shown to exaggerate the mental component score (MCS) in patients with a substantial physical disability (Scott et al., 1999) causing difficult interpretation problems, which could potentially lead to erroneous conclusions about health status (Laucis et al., 2015). The finding for the MCS compared to PCS must be considered in this light for the current study and mental health scores interpreted with caution. It is possible that participants in this study presented with lower scores for mental health due to the presence of comorbidities as well as their socioeconomic status; a possible explanation could be that both HIV and dealing with a significant health problem in poor socioeconomic circumstances are associated with mental health problems (Biglari et al., 2016; Tanaka et al., 2018).

The dysfunctional physical function, a role limited by physical and body pain found in relation to participants, has important consequences for patients with fracture non-union, as confirmed by a study that reported a significant impact in quality of life of patients with tibial non-union fractures (Haffner et al., 2016). The findings of substantial physical functioning in non-union fractures highlight the prerequisite of physiotherapy interventions for these components.

The burden associated with impairment, participation restrictions and quality of life has a human and social cost (Neogi, 2013). In addition, considering the age of most patients with non-union shown in this study, one can see they are in the economically active group. It is therefore prudent to consider ways of reducing the possibility of fracture non-union among patients with fractures. Clinical pathways are complex algorithms that involve many facets of patient care and the pathway that involves the rehabilitation of patients begins early in the continuum of care. The exploration of different interventions, such as non-invasive physiotherapy, that may attenuate the healing process of fracture may be a possible avenue to reduce the cost burden.

4.4.2.2 Cost related to health status

Factors that affect cost were considered and included the length of stay in hospital, number of re-admissions, medical and surgical procedures, amount of medication and number of therapies received, as well as the provision of assistive devices.

Often the cost efficiency within a clinical pathway is reflected in the reduction of medical costs both on the patient and on hospital (Sánchez-Hernández et al., 2016). In South Africa, public hospitals’ costs are highly subsidised by the government, particularly for low-income earners and pensioners. In this study, the direct financial outcomes were not explored in the development and implementation of this partial clinical pathway. This is contrary to other studies, which have included financial outcomes in their clinical pathway development and implementation (Lau et al., 2013; Panella et al., 2008).

In this study, 95% (n=21) of patients were surgically managed with external fixation and 86% (n=19) were managed with open reduction internal fixation (ORIF). A retrospective study in Malaysia supported external fixation as the best surgical tool to treat infected non-union fractures (Fahad et al., 2019). The author recommended external fixation as it provides stable mechanical environment, correct deformity and encourages weight-bearing (Fahad et al., 2019). In the current study, the patients managed with external fixation were also encouraged to mobilise. Apart from the benefits of the external fixation presented, a retrospective study reported more cost effective to remove external fixation and replace with ORIF intramedullary nailing (Emara et al., 2015). Antonova *et al.* (2013b) found that patients with non-union are more likely to need more than one surgery adding to the cost of care. Three (13.6%) of the participants had amputation of the lower limb as their final outcomes. Reconstruction of the non-union fracture usually is a choice for both the surgeon and the patient though it comes with costs of repetitive surgery. A cost comparative study of limb salvage and amputation of a diabetic foot found that limb salvage is costlier than amputation (Gil et al., 2013). The author highlighted that both limb salvage and amputation required rehabilitation.

In terms of medication, all the participants in this study received pain medication, 20 received antibiotics and two received anti-inflammatories. Some participants received a number of different medications including strong opioids over a prolonged period. Medication and hospital costs were significantly greater for patients with fracture non-union (Antonova et al., 2013). The length of stay for the patients with non-union fractures in this study was observed and followed-up over six months. Inpatient care by nurses was required, with 45% of participants being in traction that added to the burden of care and made them dependent on nursing care for personal care activities. Traction for non-union is costlier than ORIF in a low-income country (Parkes et al., 2017).

Three participants were in hospital for more than 20 months, while the median length of stay in hospital was four months. This presented a significant cost of care for these patients, as inpatient care is significantly more expensive than outpatient care, not only for medical care but also for rehabilitation such as physiotherapy. It has been shown that patients with non-union fractures attended all types of care including surgical care, inpatient and outpatient physiotherapy care than those without non-union fractures (Antonova et al., 2013a). The issuing of assistive devices also adds to the cost of treatment and all participants received either crutches or a wheelchair, usually at the state’s expense.

All the participants received physiotherapy for their lower limb fracture non-union. This is one of the non-invasive treatments offered along with weight-bearing exercises, pre-surgical intervention. Non-invasive therapy can also be offered in physiotherapy in the form of biophysical techniques, including high energy extracorporeal shock wave therapy, pulsed electromagnetic field, constant direct current, and low-intensity pulsed ultrasound (LIPUS) (Miller et al., 2012). These therapies provide a stimulating effect on cells that may influence bone healing although there is still controversy as to the effectiveness of LIPUS in the treatment of fractures and fracture non-union (Busse et al., 2016; Mundi et al., 2009; Pounder and Harrison, 2008; Schandelmaier et al., 2017).

Low-intensity pulsed ultrasound was not offered to patients with non-union in any of the hospitals where this study took place. LIPUS treatment is usually offered for 20 minutes each day over 8-10 weeks for up to 24 hours. The repetitive treatment with LIPUS requires patients to continue the treatment at home after discharge from hospital, so they need access to a machine at home. Therefore, the cost effectiveness of this therapy even in developed countries has been questioned in terms of the outcomes achieved, as it requires expensive equipment costing between US$1300 and $5000 per machine (Poolman et al., 2017). Although the treatment outlay is costly, the non-invasive treatment of non-union fracture is not yet established in South Africa. Currently, evidence indicates that LIPUS is still the most beneficial non-invasive treatment for the patients with non-union fractures. However, in developing countries such as South Africa, the cost of implementing this intervention must be considered in light of benefits it may provide in terms of reduced risk of disability. Other aspects of treatment were also found to be lacking in the current study. Although participants had limited roles in everyday activities and mental health problems, as identified on the SF-36, only 22% had seen an occupational therapist. There was no indication of other treatment for mental health problems or services provided for these problems. The dietician also saw 22% of participants for nutritional deficits. This intervention was provided to assist with appropriate and adequate nutrition especially when participants presented with comorbidities, such as 13% with diabetes, which requires a special diet, and 49% with HIV, which has been associated with inadequate dietary intake, nutrient loss and metabolic changes (Colecraft, 2008).

All the participants in this study attended six follow-up visits to the hospital (Hernandez et al., 2012a; Giannotti et al., 2013) throughout this research. The continuous follow-up to the hospital may have placed an extra financial burden on the participants and this has to be considered in the clinical pathway. In South Africa, long-term health issues in patients are associated with extra financial costs in terms of loss of income and the expense of attending follow up visits at the hospital. In communities with low socioeconomic status, hospital visits are an added expense that often requires hiring private transport; transport is a hidden expense. If patients do not attend follow up visits further complications may occur adding further expense to the health system (Badenhorst et al., 2018).

Implementation of clinical pathways reduced the length of hospital stay and significantly reduced follow-up visits, infrastructure and nursing costs (Müller et al., 2009). It is recommended that future enhancements be conducted in this clinical pathway study to include financial outcomes that are important in assessing the clinical care efficiency and the financial impact on both the patient and the hospital in the treatment of lower limb non-union fractures. Non-union fractures take longer to heal and therefore the cost of medical services can escalate, and coupled with the loss of income due to immobility, this increases the financial burden on the patients and hospitals.

4.4.3 Recommendation for a proposed clinical pathway for fracture non-union

A prime objective when developing a clinical pathway should be to understand the factors that are needed to inform improved care for patients. Factors identified may be addressed in clinical practice in a manner that allows holistic and cost-effective care based on the context in which it will be implemented (Brown et al., 2016). Clinical pathways are specific to a given setting and therefore for this study, should be within a context where resources are limited. One of the missing components in the arm of the clinical pathway for rehabilitation and physiotherapy established from this study is the lack of use of LIPUS, and it is proposed as an addition in the partial pathway in Figure 4. Research evidence should be used so as not to compromise the quality of care considering the most cost-effective care within the shortest possible length of stay.

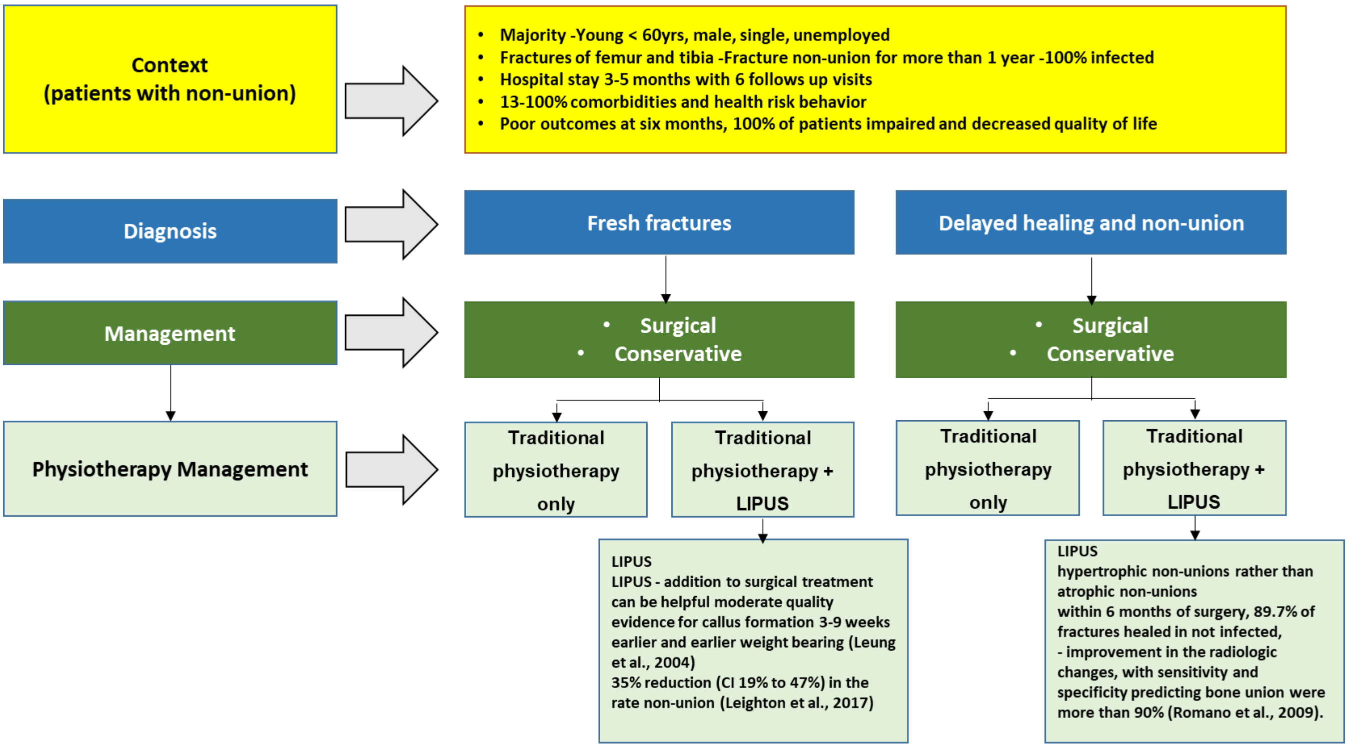

Figure 4.2: Proposed clinical pathway for physiotherapy for non-union fractures of the lower limb based on data collected at phase one

Figure 4.2 above is based only on the first phase of the process of developing a clinical pathway. Currently, the researcher has not included the other multidisciplinary team input, which is recommended for future studies. Figure 4.2 demonstrates the proposed physiotherapy clinical pathways that should be followed to maintain and improve the patients' impairments.

4.4.4 Strength and Limitations of the study

This is the first study in South Africa that investigated the factors, which need to be considered when proposing the development of a clinical pathway in lower limb non-union fractures.

The next phase in the development of a clinical pathway will involve consulting other multidisciplinary team members. However, this phase of establishing the clinical pathway and finalising a clinical pathway for lower limb non-union fractures was outside the scope of this study.

It is recommended that future studies include a multidisciplinary team to understand the full costs and final quality of life of patients. The small sample size in this study means that the data collected for this study may be insufficient and that the outcome of patients following non-union fractures is still not clearly known.

4.4.5 Conclusion

In an attempt to provide quality, healthcare clinical pathways have been suggested as a method to provide healthcare in an efficient manner. A clinical pathway is a multidisciplinary plan of care that outlines the main clinical interventions for a specific context to co-ordinate, deliver, monitor and review care (Cheah, 2000). The current study addressed Phase 1 of a clinical care pathway development for patients with fracture non-union of the lower limbs in this study provided a profile of the patients and the treatment they received in five state hospitals in Gauteng.

A number of factors including the anatomical fracture site and the socio-demographic characteristics of the patients need to be considered with a multidisciplinary team. It has been shown in this phase of the current study that these patients are receiving substantial healthcare resources including hospitalisation, a number of surgeries, high medication use and rehabilitation therapy. When a holistic view of the participants was considered it was confirmed that non-union fracture healing takes a toll on the emotional and physical functioning of the patient, and this study found that lower limb non-union fractures can significantly reduce the quality of life of patients through a host of emotional problems and impaired physical health. The patients also present with impairments, which affect activity participation according to the ICF. These health concerns may not be receiving any attention from the health team.

CHAPTER 5: PHASE 2: THE EFFECTIVENESS 0F LOW INTENSITY PULSED ULTRASOUND ON THE HEALING OF PATIENTS WITH LOWER LIMB FRACTURES

5.1 INTRODUCTION

The adverse consequences of fractures account for the majority of physical impairment post skeletal trauma due to mal-union, delayed healing or non-union. Fracture healing is a natural process but in some instances, where healing is hindered, non-union is an outcome in about 5% of patients (Zura et al., 2016). There is no spontaneous healing expected in non-union fractures (Bhandari et al., 2012), so fractures which do not unite require additional intervention including possible surgery to facilitate healing (Leighton et al., 2017). Additional intervention comes with costs for both the patient and healthcare system.

Several authors have proposed conservative management of fracture non-union because it is the cheaper option (Griffiths et al., 2015; Ebrahim et al., 2014; Nandra et al., 2016). Research indicates low quality evidence that LIPUS accelerates fracture union and that it does initiate healing, which may influence managing non-union fractures (Ebrahim et al., 2014; Griffiths et al., 2015; Nandra et al., 2016). Low intensity pulsed ultrasound has been found to be preferable to other non-invasive treatments, such as extracorporeal shock wave therapy and electrical stimulation, as it can be continued at home post discharge and compliance rates have been reported as high when using a daily treatment session duration of only 20 minutes a day (Malizos et al., 2006). Although the equipment costs for LIPUS are relatively high, the total cost per patient is still lower than surgical intervention (Heckman and Sarasohn-Kahn, 1997).

Non-union fractures treated with LIPUS require an average of five months to heal (Dijkman et al., 2009a). Evidence showed that LIPUS treatment is more effective in reducing healing time in fractures with a long natural healing tendency, such as tibial fractures and in patients with comorbidities and health risk behaviours where the natural healing tendency was delayed (Rutten et al., 2016). The findings of one of the studies, reported in a systematic review, showed healing parameters in cortical bridging, callus formation and weight bearing as a result of LIPUS treatment;

however, this difference was non-significant (Martinez de Albornoz et al., 2011). Importantly, this systematic review identified difficulties in the study designs that influenced the quality and comparability of the studies thus making it difficult to conclude on the effects of LIPUS. Another systematic review and meta-analysis study supported the use of LIPUS for non-union fractures soon after surgery (Leighton et al., 2017). The authors reported an average success rate in LIPUS, which was higher than that of surgical treatment of non-infected non-union fractures. A sub-analysis in a systematic review indicated the possibility that LIPUS may be more effective in improving healing when fractures are surgically managed (Leighton et al., 2017). Studies that have used LIPUS have had good compliance and acceptance by patients who experience few adverse effects (Griffin et al., 2014b). The main focus of this study was to establish the effectiveness of LIPUS in patients with lower limb fractures living with comorbidities.

5.1.1 Problem Statement

Despite the application of improved technology in the surgical and medical management of fractures to facilitate healing, non-union fractures are still prevalent. Additionally, comorbidities such as HIV/AIDS, diabetes and smoking have a negative impact on fracture healing. It was clear from Part 1 of Phase 1 that higher prevalence of comorbidities affects patients with non-union in the South African context, and previous studies using LIPUS treatment have not reported such a high prevalence of comorbidities and health-related risk factors.

This study sought to determine the quality of life of the participants and record the existing comorbidities. From Phase 1 of the study, it was established there was a 13.3% prevalence for diabetes, 40.9% for HIV, and 100% for participants with non-union fracture presenting with smoking as a health risk factor. This is much higher than the prevalence of diabetes and health risk factors reported in the literature (Busse et al., 2016; Zura et al., 2015). With respect to these comorbidities and health risk behaviours, the risk of patients having delayed fracture healing and non-union can be calculated using the Pre-Surgical Non-union (PSN) score (Calori et al., 2008). Non-union scoring system (NUSS) developed by Calori et al, 2008, included comorbidities in their scoring. The PSN score is the score calculated from the NUSS before the patient goes for theatre and is mainly the comorbidities score. These comorbidities have been found to add between 10 to 20 points to the risk for non-union fractures (Calori et al., 2008).

An added comorbidity in this group of patients was HIV. There are no published studies on the use of LIPUS for fracture management in people living with HIV. Studies on patients with HIV and fracture healing show evidence of impeded blood supply to the bone, which negatively impacts on bone remodelling (Richardson et al., 2008). Other factors related to HIV complications include suboptimal nutrition, the effects of anti-retroviral drugs and wound infection. The prevalence of osteoporosis in patients with HIV also means that fracture rates may be higher among people living with HIV (Yang et al., 2013).

It was, therefore, important to establish the effectiveness of LIPUS on fracture healing in patients who have undergone surgical treatment and in patients with a non-union outcome in the presence of these comorbidities and health risk factors. The study is important, as the use of LIPUS in South Africa in public healthcare has not been reported for fracture healing.

5.1.2 The Purpose of the Study

Non-invasive low-intensity pulsed ultrasound (LIPUS) treatment may enhance the mechanical properties of callus formation and reduce the healing time of fractures as well as addressing healing in fracture non-union. Reducing the fracture healing time and facilitating fracture healing may influence associated disability and socioeconomic costs in patients and their quality of life. Additionally, understanding any difference in the effects of LIPUS in a subset of patients with comorbidities, including immune-suppressed patients, will contribute to an area where little is known.

5.1.3 Aim of the Study

The aim of this study was to determine the effect of LIPUS on healing in lower limb fractures for patients managed surgically in public healthcare hospitals in Gauteng, South Africa.

5.1.4 Objectives

- To compare fracture healing in lower limbs between patients managed surgically using real or sham low-intensity pulsed ultrasound (LIPUS).
- To determine the change in outcomes related to fracture healing in lower limbs (including patients with non-union fractures) for patients managed surgically and with real or sham low-intensity pulsed ultrasound (LIPUS).
- To establish the influence of demographic, medical, health status variables and health risk behaviour on fracture healing.

5.1.5. Null hypothesis

There will be no significant difference in the healing of lower limb fractures for patients (including patients with fracture non-union) managed surgically and with real low intensity pulsed ultrasound (LIPUS) compared to those patients managed surgically and treated with sham LIPUS.

5.1.6 Alternative hypothesis

Fracture healing in patients with lower limb fractures (including patients with non-union fractures) managed with LIPUS will be accelerated compared to patients managed only surgically and with sham LIPUS.

5.2 METHODOLOGY

5.2.1 STUDY DESIGN

A double-blinded experimental randomised control trial (RCT) design was used to evaluate the effectiveness of LIPUS by comparing its effect using an intervention and control groups.

5.2.2 RESEARCH SETTING

Data were collected at two state academic hospitals in Pretoria, Steve Biko Academic Hospital (SBAH) and Kalafong Academic Hospital. These hospitals were chosen because they are big academic hospitals, which give access for research purposes.

In addition, both hospitals have large orthopaedic units that consist of 160 beds between them. Both hospitals are tertiary academic hospitals that receive referrals from neighbouring primary hospitals and surrounding provinces with limited resources. As the hospitals are tertiary, they do not admit patients for long stay, but provide follow-up appointments after six weeks for consultation. However, the patients continue with physiotherapy treatment on a regular basis for three to four weeks, depending on the severity of the problem.

5.2.3 PARTICIPANTS SELECTION

5.2.3.1 Sampling and sample size calculation

A consecutive sampling method was used to recruit patients. Ninety participants had 80% power to detect a significant difference between the participants with or without LIPUS at the 0.05 level of significance. This meant that the study required a minimum of 90 patients to be recruited and randomly allocated with a minimum of 45 participants for treatment with machine A (Group A) and a minimum of 45 for treatment with machine B (Group B). Participants were recruited sequentially as they were admitted to the orthopaedic units. Baseline assessments were carried out on 115 participants; 58 participants were randomly allocated using a computer generated list to Group A and 57 to Group B.

5.2.3.2 Sample selection

All the patients admitted with lower limb fractures immediately after surgical management, including re-admission due to fracture non-union, were included in the study.

Inclusion Criteria

Patients were included in the study if they:

- had lower limb fractures that were managed surgically

  The presence of internal fixator, i.e. the plates and screws, does not represent contra-indication to the treatment (Masssari et al., 2009; Kocaoğlu et al., 2011)

- were over the 18 years of age and gave informed consent.

Exclusion criteria

Patients were excluded from the study if they:

- had multiple fractures (more than one fracture in one bone and/or limb)
- resided outside a 10 km radius from the hospitals used in the study, or resided outside Gauteng Province to enable follow-up.

5.2.3.3 Randomisation process

Assignment to either the control or the intervention group was done using a computer-generated list. One hundred and fifteen numbers were randomly selected to the intervention or control group. Those treated by machine A were named Group A and those treated by machine B were Group B. The researcher and the research assistant did not know which machine offered real treatment and which one gave sham treatment. The patient who was seen first was allocated the number 1, as already given. If number 1 was in Group A, they received treatment from machine A and if in Group B, they received treatment from machine B. The researcher and assistant communicated about the grouping and allocation but were blinded to the treatment allocation.

Both patients and researchers were blinded to the intervention assignment. Double blinding was made easy by labelling the LIPUS machines A and B by the supplier. The machines were identical and had pre-set treatment settings. The researchers were not aware which machine had true LIPUS or sham LIPUS. Sham LIPUS meant that the machine did not produce ultrasound, thus acted as control. The participants were allocated to either machine A or B with no information of which machine had true LIPUS. The double blinding was intended to prevent bias. Computer-generated random numbers with group allocation were contained in a sealed envelope and participants would pick an envelope which would assign them to either the control or intervention group upon agreeing to participate in the study. This allocation process was repeated until the sample size was reached. The concealed allocation process helped to minimise bias. After the Radiologist had interpreted all the results, the technician who kept the information about the machine outputs, revealed that machine A was the intervention and machine B was sham.

5.2.4 OUTCOME MEASURES

5.2.4.1 Demographic and Intervention sheet

A demographic questionnaire, which included personal demographics, medical history and captured the interventions being received, was drawn up by the researcher and used with each participant (Annexure 9).

5.2.4.2 Radiographic Methods

In this study, radiographic methods were used to assess fracture healing, as X-rays were routinely taken and were available at the research sites for patients with fractures. X-rays were taken at admission, post operation, at six weeks and 18 weeks if the patient was still attending follow-up treatment sessions. Unfortunately, we were not allowed to expose patients to additional radiation, therefore only routine radiographs were used. The use of X-rays is the quickest and easiest method to determine fracture healing in a continuous manner, which can be interpreted by radiologists and orthopaedic surgeons (Eastaugh-Waring et al., 2009). According to literature, a number of different measures should be used to assess fracture healing when using X-rays (Morshed, 2014). In this study, cortical bridging or number of cortices bridged by callus, callus formation and the absence of a fracture gap were used together to rate the overall healing of the fractures (Azevedo Filho et al., 2017; Hungri and Mercadante, 2013; Kooistra et al., 2010).

5.2.4.2.1 Measuring of callus formation

Callus formation can be assessed as either none or present, fair, abundant, maturing, or remodelled (Kooistra et al., 2010). However, in this study since the assessment was completed at 18 weeks, callus formation was only considered as either absent (none) or present; this was because in this study sample, callus had not reached a stage for further assessment. The callus formation was assessed on standard X-rays obtained during routine follow up (Azevedo Filho et al., 2017). Eighteen weeks was projected for establishing the effectiveness of the intervention not fracture healing. A fracture takes 6 – 8 weeks to heal, because the study population included patients with comorbidities a longer duration was proposed.

5.2.4.2.2 Measuring cortical bridging and quantifying the number of cortices bridged.

Identifying the number of cortices bridged was recommended as a method of determining radiographic union for assessing consolidation (Kooistra et al., 2010). Fracture consolidation was measured as the presence of at least three consolidated cortices observed in two radiographic views (anteroposterior and lateral), as suggested by Hungri and Mercadante (2013). Each cortex is attributed points ranging from one to four (Azevedo Filho et al., 2017) and assigned a score for a given set of anterior posterior and lateral radiographic views based on the assessment of healing in each of the four cortices visible on these projections.

5.2.4.2.3 The absence of a fracture gap

Primary healing of fractures can occur through either contact healing or reduction of the fracture gap. If the gap between bone ends is less than 0.01 mm the fracture can heal by contact healing (Marsell and Einhorn, 2011). Radiographic determination of the fracture gap is therefore needed to observe if a fracture gap is present or not, as the presence of such will delay fracture healing (Indu et al., 2014). Fracture gap is the space between the two ends of the bones (Marsell and Einhorn, 2011).

5.2.4.2.4 Overall rating of healing

Since remodelling of the fracture callus does not commence until sufficient stability of the fracture has been achieved, fracture union is assessed using plain lateral and anterior-posterior view of the X-rays to determine the time taken to reach maximum callus diameter as measurement of overall healing or clinical union of the fracture (Eastaugh-Waring et al., 2009). The radiologist judges overall healing before maximum callus is reached and indicates if the lack of a peak in the callus index is an indicator of delayed fracture healing (Eastaugh-Waring et al., 2009).

5.2.5. RESEARCH PROCEDURE

5.2.5.1 Recruitment and assessment

After ethical clearance and permission to complete the study at the hospitals were obtained, the admission book was used to review the patients admitted with lower limb fractures in the orthopaedic wards of both hospitals. Patients eligible for the study were subsequently identified and recorded in the data collection book; the X-rays of the identified patients from the record books were accessed to confirm the diagnosis. Patients were allocated to the intervention or control group using a computer-generated random sampling process. Prior to the initial treatment, patients' records and X-rays were reviewed for baseline assessment. Initial diagnosis, fracture type, surgical management and medication given were collected from the records and the X-rays.

5.2.5.2 Intervention

The intervention and control groups were treated concurrently with LIPUS. The presence of internal fixator, i.e. the plates and screws, does not represent contra-indication to the treatment (Masssari et al., 2009; Kocaoğlu et al., 2011). A qualified physiotherapist was trained in the use of the Enraf-Nonius LIPUS machine, and served as the research assistant for the study. The research assistant assisted with recruitment of patients in the study, and both the researcher and the research assistant applied the LIPUS intervention. The equipment used for this study was Enraf-Nonius Sonopuls 690StatUS Low-Intensity Pulsed Ultrasound (Manufactured in 2012). Treatment of the fracture was conducted on the fracture area for 20 minutes on alternate days.

Two identical LIPUS machines were available. One machine was functional and provided LIPUS intervention and the other machine was set up as a sham machine, which did not provide LIPUS. Both machines were identical and labelled A and B. The machine settings were done by the technicians at Mediotronics, the company who supplied the machines. The information of each machine was kept in an inventory book in a safe. The treatment effect on the sham machine was disabled. The settings were given to the technicians by the researcher. Both machines were showing similar functionality on the display screen. On completion of the study, the researcher requested the technician to reveal which machine was intervention or sham. The researcher and the research assistant were blinded as to which was the sham machine, only the technician knew which machine was providing real LIPUS treatment. Both machine A and B were used for intervention or sham, depending on the group the patient was assigned to.

The baseline assessment included reading of the admission record and X-ray of the patient and confirming the diagnosis. If a patient was diagnosed with lower limb fracture and managed surgically, the patient was recruited to participate in the study.

The information sheet (Annexure 7D) was given to the patient to read what the research entailed and they were then requested to complete the consent form (Annexure D). Patients' treatment started day one post-operation, or sometimes one to two days later as the some requested no treatment as they were in pain post operatively.

Patients eligible for the study were treated every second day for 20 minutes. The total treatment period of each patient was 40 days during which participants received 20 treatments, with either machine A or B, depending on their group assignment. Both machines were pre-set at an intensity of 0.03 W/cm^2, frequency of 1.5 MHz and pulse width of 200 μs (Harrison et al., 2016). The duration of the treatment was the same for both machines.

The treatment time allocated in this study was the same as in previous studies to accelerate fracture healing, but treatment frequency was alternate days instead of every day. The reason for the difference in treatment frequency was the availability of the LIPUS machines. On discharge, participants were followed up and the researcher applied continuous LIPUS at home, or participants were requested to come to the hospital for treatment and the researcher reimbursed the travelling expenses. Where applicable, the researcher travelled to the participants' homes as the machines could not be kept at the patients' homes for them to apply the therapy, as the other studies suggested (Miller et al., 2012). For this study, it was unsafe to leave the machine in the participants' homes as many participants lived in low resourced areas where theft was a reality (Bhorat et al., 2017).

5.2.5.3. Data Collection

Data were collected in relation to the patient's demographics. The outcome measures (callus formation, cortical bridging, and fracture gap) for fracture healing were determined from patients' X-rays taken at six, 12 and 18 weeks after the patients' LIPUS treatment started. The X-rays films were pre-collected by the researcher for one hospital where there were no online services; in the other hospital, the electronic X-ray version was used and in this case, X-ray numbers were taken to the radiology department for analysis. The researcher arranged the date and time to meet at a specific hospital for data analysis. The radiologist who interpreted the X-rays' findings was also blinded. The data from each X-ray were recorded on a data sheet, which included the presence of callus, the presence of cortices bridged according to a score of one to four cortices, and the presence or absence of a fracture gap. The overall fracture healing time was recorded to capture if healing had taken place at six, 12 and 18 weeks post fracture.

5.2.6. DATA ANALYSES

Data were cleaned and coded in an Excel spreadsheet and sent to the statistician for assistance with the analysis. Demographic data were analysed using descriptive statistics. A per-protocol analysis that included the data available for only participants with X-rays at each time was completed for the between and within group changes. An intention to treat (ITT) analysis indicated similar results thus, the per-protocol analysis is presented in the results with the ITT analysis in Annexure 10. The difference in fracture healing between those managed with LIPUS compared to those managed with a sham machine was analysed using Pearson's Chi-square test. The variables related to fracture healing analysed included callus formation, cortices bridged, and fracture gap, as well as overall healing at six, 12, and 18 weeks.

The percentage change in fracture healing within the intervention and control groups was observed. The McNemar Chi-square test was used to analyse the within group fracture healing change at six, 12 and 18 weeks. Data to determine the association between fracture outcomes and personal and medical demographics, comorbidities as well as risk health behaviours were analysed using logistic regression and presented as odds ratios and 95% confidence intervals.

Pearson's Chi-square test was used to determine association between two categorical variables in fracture healing for participants with non-union fractures in the control and intervention groups. The change in fracture healing within the intervention and control group was compared using the McNemar Chi-square test. The difference in fracture healing between the two groups of participants presenting with non-union fractures were analysed using Fisher's Exact test (and where the numbers were small, Pearson's Chi-square test). The univariate logistic regression was used to analyse demographic, medical comorbidities and health status variables. Multivariate logistic regression was used to analyse the time frame for healing of the fractures at six weeks, 12 weeks and 18 weeks.

5.2.7 ETHICAL CONSIDERATIONS

Ethical clearance and approval from the Human Resource Ethics Committee at the University of the Witwatersrand (M150236) (Annexure 5) and University of Pretoria (349/2017) (Annexure 6) were obtained prior to the commencement of the study. Furthermore, permission to conduct the study from Kalafong Hospital (Annexure 7) and the SBAH (Annexure 8) was granted. Written consent was also obtained from the participants to participate in the study. The participants were informed of the objectives of the study, and an information sheet (Annexure 4A) was provided and signed for informed consent (Annexure 4B). The patients were assured of confidentiality, and that all the information obtained would remain confidential and anonymous; coding was used on all records to hide the identity of the participants. The participants were informed of their right to withdraw from the study at any time and that their withdrawal would not have any effect on their planned treatment.

5.3 RESULTS

5.3.1 Introduction

This section describes the results from the randomised controlled trial to establish the effect of the LIPUS intervention on fracture healing of patients with lower limb fractures managed surgically (intervention group) compared to those patients managed by surgery and sham LIPUS (control group). Results of the measurements taken at baseline, six, 12 and 18 weeks are given for the between and within group analysis. The influence of other factors on fracture healing is also presented.

In the intervention group, one patient left the province within three days, and two patients were excluded from the study at the second week post discharge, as they had no electricity to plug in the machine at home. For nine patients, the X-rays were missing and they could not have new X-rays taken because that process was deemed unethical; the results for these patients were thus lost to analysis. In the control group, one patient withdrew at week two and seven patients had missing X-rays. Ninety-four patients were therefore included for analysis, with 45 patients in the intervention group and 49 patients in the control group.

Check-up X-rays were not completed at six weeks for four patients, at 12 weeks for 33 patients and 13 patients at 18 weeks, which led to further loss to follow up. X-rays were available for 57 patients at 12 weeks and only 44 patients at 18 weeks.

The recruitment and loss to follow up for all participants is presented in Figure 5.1

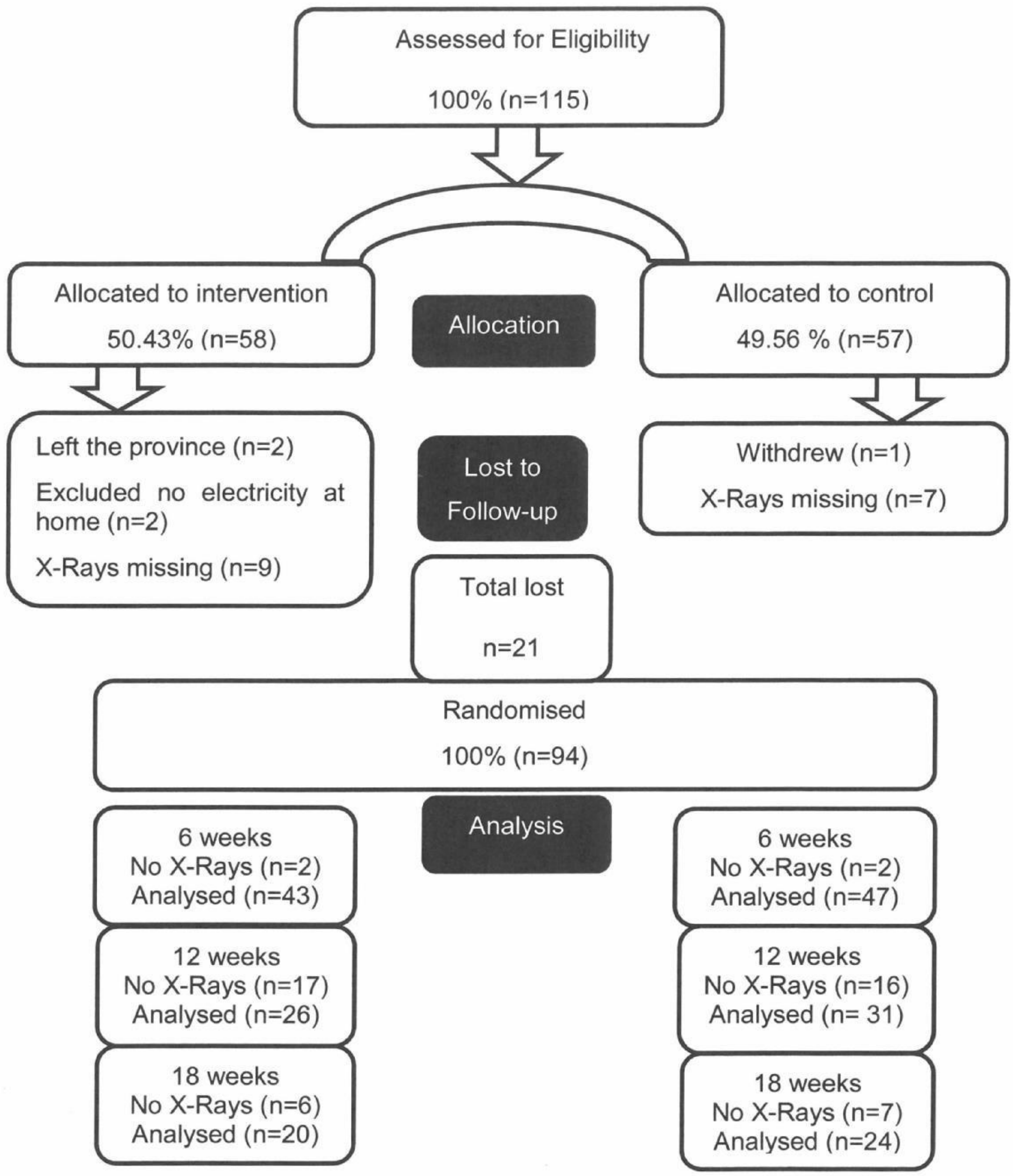

Figure 5.1: Consort flow diagram of participants throughout the study showing loss to follow up (n=115)

5.3.2 Demographics

5.3.2.1 Personal and medical demographics

There were more male participants (68%) than females with lower limb fractures. The female participants were, on average, 10 years older than the males; the youngest patient was 18 years, and the oldest was 82 years old, both of whom were in the female group (Table 5.1).

Table 5.1: Demographic characteristics of the participants (n=115)

	Total Group		**Intervention Group**	**Control Group**	**p-value**
Gender	n (%)				
Female	37 (32.17)		20 (34.48)	17 (29.83)	0.544
Male	78 (67.83)		38 (65.52)	40 (70.17)	
Age	Mean Age (SD)	Min-Max	Mean Age (SD)	Mean Age (SD)	
Female	48.86 (18.33)	18-82	50.26 (20.77)	47.38 (15.81)	0.243
Male	38.54 (13.18)	19-73	39.94 (13.06)	37.65. (14.82)	
Total	41.86 (15.72)	18-82	43.50 (15.73)	40.62 (15.66)	

The study participants were quite similar in age between the intervention and control group.

Table 5.2 shows a higher percentage of femur fractures (60%) compared to other fractures in the lower leg. Open reduction with internal fixation (ORIF) (78.26 %) was the most common surgical management used, with just over 20% of participants being treated using external fixation.

Table 5.2: Frequency and percentage of type of fractures and their management (n = 115)

	Total group	Intervention Group	Control group	p-value
Type of fracture	n(%)			
Femur	69 (60.00)	34 (58.62)	35 (61.40)	0.656
Tibia	24 (20.87)	12 (20.68)	12 (21.05)	
Tibia and Fibula	22 (19.13)	12 (20.68)	10 (17.54)	
Type of management				
ORIF	90 (78.26)	45 (77.58)	45 (78.94	0.821
Ext-Fixation	25 (21.74)	13 (22.41)	12 (21.06)	

There was a similar number of the fracture types and management in both intervention and control groups

Figure 5.2 shows the mean age of the participants according to the anatomical fracture type in the intervention and control groups. There was no significant difference between the intervention and control groups for these variables.

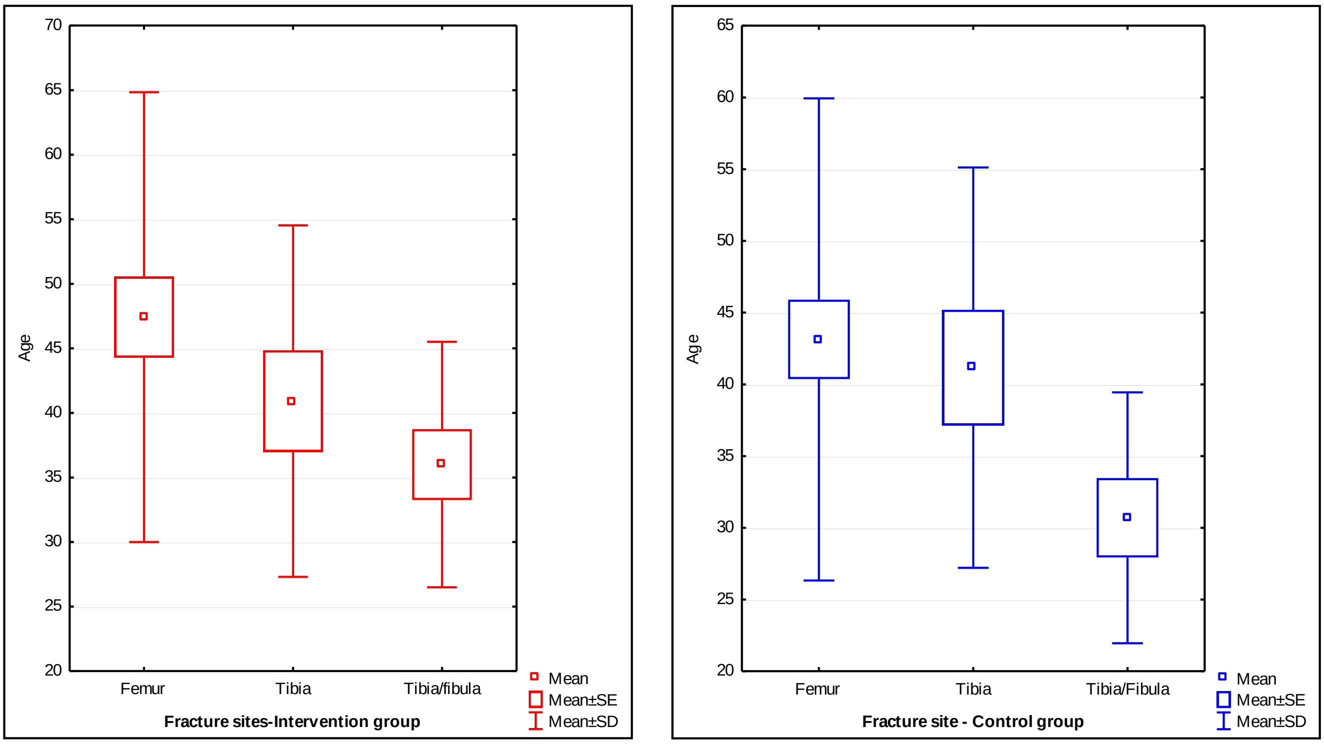

Figure 5.2 Mean age of participants by fracture site for the intervention and control groups

The mean age of participants was higher in the intervention group in all fracture sites. In both groups, the mean age of participants with fractures in the femur was slightly higher at 47.15 (±14.12) years for the intervention group than the 42.49 (±18.23) years for the control group, although this difference was not significant (p=0.604). The youngest mean age was for the participants with fractures of the tibia and fibula in the control group at 30.70 years.

5.3.2.2 Health status

Table 5.3 below presents medical comorbidities of the participants and other factors that could affect their health status. The participants presented with several comorbidities, with smoking (60.87%) and a positive HIV status (43.48%) being the most prevalent; just over a quarter of the participants were hypertensive or presented with diabetes and two participants had cancer (Table 5.3).

Table 5.3: Frequency and percentages of medical factors, comorbidities and health risk factors (n = 115)

Comorbidities	Total n (%)	Intervention n (%)	Control n (%)	Chi-square (p-value)
Smoking				
Smokers	70 (60.87)	24 (41.39)	20 (35.08)	0.465
Non-smokers	45 (39.13)	34 (58.61)	37 (64.92)	
HIV Status				
Positive	50 (43.48)	26 (44.83)	25 (43.85)	1.000
Negative	65 (56.52)	32 (55.17)	32 (56.15)	
Cancer				
Cancer	2 (1.74)	1 (1.75)	1 (1.75)	1.000
No cancer	113 (98.26)	57 (98.27)	56 (98.24)	
Bone unity				
United	98 (85.22)	50 (86.20)	48 (84.22)	0.838
Non-union	17 (14.78)	8 (13.80)	9 (15.78)	
Diabetic status				
Diabetic	31 (26.96)	17 (29.31)	14 (24.57)	0.520
Non-diabetic	84 (73.04)	41 (70.69)	43 (75.43)	
Blood Pressure status				
Hypertensive	29 (25.22)	35 (60.34)	45 (78.94)	0.008**
Non-hypertensive	86 (74.78)	24 (39.66)	12 (21.06)	

Significance p ≤0.01**

Of the 17 participants with non-union fractures, the percentage of comorbidities were similar to those in Phase 1, Part 2 of the study with comorbidities of HIV at 53%, and diabetes and hypertension at 23.52%. Approximately 76.4% of the participants with non-union fractures were current smokers. The two groups were comparable in terms of the comorbidities participants presented with except for hypertension; there were significantly more participants in the control group with hypertension (p=0.008).

5.3.3. Lower limb fracture outcomes

5.3.3.1 Comparison of fracture healing between the intervention and control groups over time

The difference in fracture healing between the two groups of participants (the intervention and control groups) was analysed using the Pearson’s Chi-square test. The variables related to fracture healing that were analysed, which included callus formation, cortices bridged and fracture gap, as well as overall healing at six, 12, and 18 weeks post treatment. As shown in the consort diagram (Figure 1), patients with available X-rays were assessed further. X-rays were not available for four of the 94 participants at six weeks, but since they were available for these participants at 12 and 18 weeks, they were retained in the study. Ninety participants were observed at six weeks for between group analysis, 57 at 12 weeks and 44 at 18 weeks.

5.3.3.1.1 Callus formation

Table 5.4 displays callus formation comparisons between the intervention and control groups. The radiologist assessed whether there was callus formation present on the X-rays. At six weeks, there was no significant difference in the presence of callus formation between the intervention and control groups, although a higher percentage (72%) in the intervention group had some formation of callus compared to the control group (57%). At 12 weeks’ callus formation increased progressively, with 85% of the intervention group having callus compared to 77% of the control group.

At 18 weeks, a higher percentage of the control group (100%) than the intervention group (95%) had callus formation, thus callus formation was observed in all the participants except one in the intervention group at 18 weeks. There was no significant difference in the intervention and control groups in callus formation at 12 and 18 weeks (Table 5.4).

Table 5.4: Callus formation in the lower limb for the intervention and control groups n=90

	Total n (%)	Intervention n (%)	Control n (%)	Pearson's Chi-square (p-value)
Six weeks				
Observed	90 (100)	43 (100.00)	47 (100)	
Callus formed	58 (64.44)	31 (72.09)	27 (57.45)	0.147
No callus formed	32 (35.56)	12 (27.91)	20 (42.55)	
12 weeks				
Observed	57 (100.00)	26 (100.00)	31 (100.00)	
Callus formed	46 (80.70)	22 (84.62)	24 (77.42)	0.493
No callus formed	11 (19.30)	4 (15.38)	7 (22.58)	
18 weeks				
Observed	44 (100.00)	20 (100.00)	24 (100.00)	
Callus formed	43 (97.73)	19 (95.00)	24 (100.00)	0.268
No Callus formed	1 (2.27)	1 (5.00)	0 (0.00)	

Callus formation was evident in the intervention group at 6 and 12 weeks compared to the control group. However, the control group had 100% callus formation in the patients that remained, although it was not statistically significant.

5.3.3.1.2 Number of cortices bridged

The difference in the number of cortices bridged was calculated using Pearson's Chi-square test to show the effect of low-intensity pulsed ultrasound on time to heal between the intervention and control groups, as shown in Table 5.5. The radiologist observed the cortices bridged, which involved identifying the presence of at least three consolidated cortices observed in the anterior and posterior radiographic view.

Table 5.5 Number of cortices bridged in lower limb fractures for the intervention and control groups (n=90)

	Total n (%)	Intervention n (%)	Control n (%)	Pearson's Chi-square (p-value)
Six weeks				
Observed	90 (100.00)	43 (100.00)	47 (100.00)	
No cortices	68 (75.56)	33(76.74)	35 (74.47)	0.986
1 Cortices	15 (16.67)	7 (16.28)	8 (17.02)	
2 Cortices	5 (5.56)	2 (4.65)	3 (6.38)	
3 Cortices	2 (2.22)	2 (2.33)	2 (2.13)	
12 Weeks				
Observed	57 (100.00)	26 (100.00)	31 (100.00)	
No cortices	16 (28.07)	9 (34.62)	7 (22.58)	0.322
1 Cortices	20 (35.09)	6 (23.08)	14 (45.16)	
2 Cortices	16 (28.07)	9 (34.62)	7 (22.58)	
3 Cortices	5 (8.77)	2 (7.69)	3 (9.68)	
18 weeks				
Observed	44 (100.00)	20 (45.45)	24 (54.55)	
No cortices	17 (38.64)	6 (30.00)	11 (45.83)	0.676
1 Cortices	9 (20.45)	5 (25.00)	4 (16.67)	
2 Cortices	11 (25.00)	5 (25.00)	6 (25.0)	
3 Cortices	6 (13.64)	3 (15.00)	3 (12.5)	
4 Cortices	1 (2.27)	1 (5.00)	0 (0.00)	

At six and 12 weeks respectively, no participants showed four cortices in either group. In both the intervention and control groups, there was no significant difference between the groups for this variable at six or 12 weeks. At 18 weeks, there were more participants initially observed for cortices in the control group (n=24; 54.55%)

than in the intervention group (n=20; 45.45%). Conversely, the fourth cortex was present at 18 weeks on the intervention group (n=1; 5%), although this was not statistically significant (Table 5.5).

5.3.3.1.3 Fracture gap

The fracture gap present at the three time points was measured and the difference between the two groups was calculated using Pearson's Chi-square test, as shown in Table 5.6. At six weeks, the fracture gap was still clearly visible for both the intervention and control groups in 35 participants (81.40%) and 38 participants (80.85%) respectively, with no significant difference between the groups.

Table 5.6 The presence of a fracture gap for intervention and control group n=90

	Total n (%)	Intervention n (%)	Control n (%)	Pearson's Chi-square (p-value)
Six weeks				
Observed	90 (100.00)	43 (100.00)	47 (100.00)	
Gap	73 (81.11)	35 (81.40)	38 (80.85)	0.947
No Gap	17 (18.89)	8 (18.60)	9 (19.51)	
12 weeks				
Observed	57 (100.00)	26 (100.00)	31 (100.00)	
Gap	27 (47.37)	11 (42.31)	16 (51.61)	0.483
No gap	30 (52.63)	15 (57.69)	15 (48.39)	
18 weeks				
Observed	44 (100.00)	20 (100.00)	24 (100.00)	
Gap	26 (59.09)	11 (55.00)	15 (62.50)	0.614
No Gap	18 (40.91)	9 (45.00)	9 (37.50)	

The findings were similar at 12 weeks, where the fracture gap was visible in 11 (42%) participants of the intervention group and in 16 (52%) of the control group. There was a reduction in the number of participants with a visible fracture gap. There was no significant change in the fracture gap in both the interventions and control groups at 18 weeks (p=0.61).

5.3.3.1.5 Overall state of healing

The difference in the overall state of healing between the intervention and control groups was analysed using Pearson's Chi-square test. At six weeks, there were no signs of healing in either the intervention or control group, with no significant difference between the groups (p=1.00).

Table 5.7 Overall healing of fractures between the intervention and control groups n=90

	Total n (%)	Intervention n (%)	Control n (%)	Pearson's Chi-square (p-value)
Six weeks				
Observed	90 (100.00)	43 (100.00)	47 (100.00)	
Healed	0 (100.00)	0 (100.00)	0 (100.00)	1.00
Not Healed	90 (100)	43 (100.00)	47 (100.00)	
12 weeks				
Observed	57 (100.00)	26 (100.00)	31 (100.00)	
Healed	4 (7.02)	2 (7.69)	2 (6.45)	0.855
Not healed	53 (98.92)	24 (92.31)	29 (93.55)	
18 Weeks				
Observed	44 (100.00)	20 (100.00)	24 (100.00)	
Healed	2 (4.55)	1 (5.00)	1 (4.17)	0.895
Not Healed	42 (95.45)	19 (95.00)	23 (95.83)	

** p<0.01, * p<0.05

The percentage of healing was lower at 18 weeks than at 12 weeks, as there was a 5% healing rate within the intervention group and 4% within the control group, although the difference was not statistically significant (Table 5.7).

Although there was no statistically significant difference between the groups for any assessment periods, the analysis indicates that the intervention group had a higher percentage of participants with callus formation at six weeks, which was slightly less by 12 weeks, and by 18 weeks, the two groups had similar callus formation. There was a higher percentage of participants with no fracture gap at 12 and 18 weeks and a higher percentage of participants with cortices bridged at 18 weeks in the intervention group. Overall, healing was similar for both groups for all assessment periods.

5.3.3.2 Non-Union Fractures – Sub-Analysis

From the study cohort, the participants with non-union fractures were analysed separately to explain how non-union fractures performed in the presence of other comorbidities in lower limb fractures. Literature supports the use of LIPUS for non-union fractures soon after surgery, so the outcome for participants in the study with non-union fractures were analysed separately.

5.3.3.2.1 Comparison of healing for participants with non-union fracture between the intervention and control groups over time

Seventeen participants in the study presented with non-union fractures. Six were randomly treated with LIPUS and six randomly on the control group. The difference in fracture healing between the two groups of participants presenting with non-union fractures were thus analysed using Fisher's Exact test, as some groups had less than five participants with callus formation (Table 5.8).

Twelve of the participants had X-rays available at six weeks, and per protocol analysis of fracture healing for this subgroup was completed at six, 12 and 18 weeks for callus formation, cortices bridged and presence of a fracture a gap (Tables 5.8; 5.9; 5.10). None of the participants in the intervention or the control group achieved overall fracture healing in the 18-week period, so results for overall healing are not presented.

Callus formation

At six weeks, there was no significant difference in the presence of callus formation between the intervention and control group of those with non-union fracture, although one more participant in the intervention group had some formation of callus.

Table 5.8 Callus formation in the lower limb of participants with non-union in fractures the intervention and control groups (n=12)

	Total n (%)	Intervention n (%)	Control n (%)	Fischer's Exact (p-value)
Six weeks				
Observed	12 (100)	6 (100.00)	6 (100.00)	
Callus	3 (55.55)	2(28.57)	1 (16.67)	0.164
No callus	9 (44.45)	4(71.43)	5 (83.33)	
12 weeks				
Observed	11 (100.00)	6 (100.00)	5 (100.00)	
Callus	6 (80.70)	4(71.43)	2 (40.00)	0.005**
No callus	5 (19.30)	2 (28.57)	3 (60.00)	
18 weeks				
Observed	10 (100.00)	6 (100.00)	4 (100.00)	
Callus	10 (100)	6 (100.00)	4 (100.00)	1.00
No Callus	0 (0.00)	0 (0.00)	0 (0.00)	

** $p<0.01$, * $p<0.05$

At 12 weeks, callus formation increased progressively with 71% of the intervention group having callus compared to 40% of the control group. The difference at this stage was significant (p=0.005).

At 18 weeks, all the participants in the control group (100%) and in the intervention group had callus formation. There was no significant difference in the intervention and control groups in callus formation at 18 weeks (Table 5.8).

Cortices bridged

The differences in the number of cortices bridged were calculated for participants with non-union fractures, as shown in Table 5.9. Cortices bridged were observed and the presence of at least three consolidated cortices were observed in the anterior and posterior radiographic view. At week six, one participant in each of the two groups had one cortex bridged with no difference between the groups (Table 5.9). By week 12, 66% of the intervention group had one cortex bridged and 16% had two cortices bridged. None of the participants assessed in the control group had cortices bridged, with the exception of one participant who had changed from one to three cortices bridged. There was therefore a significant difference between the groups' (p=0.001) cortices.

Table 5.9: Cortices bridged in the lower limb of participants with non-union in the intervention and control groups n=12

	Total n (%)	Intervention n (%)	Control n (%)	Fischer's Exact (p-value)
Six weeks				
Observed	12 (100.00)	6 (100.00)	6 (100.00)	
No cortices	10 (75.56)	5(94.44)	5(94.44)	1.000
1 Cortices	2(16.67)	1(5.56)	1(5.56)	
2 Cortices	0(0.00)	0(0.00)	0(0.00)	
3 Cortices	0(0.00)	0(0.00)	0(0.00)	
12 Weeks				
Observed	11(100.00)	6(100.00)	5(100.00)	
No cortices	5(45.45)	1(16.66)	4(80.00)	0.001**
1 Cortices	4(36.36)	4(66.67)	0 (0.00)	
2 Cortices	1(9.00)	1(16.66)	0 (0.00)	
3 Cortices	1(9.00)	0 (0.00)	1 (20.00)	
18 weeks				
Observed	10 (100.00)	6 (100.00)	4 (100.00)	
No cortices	5(50.00)	2 (33.33)	3 (75)	0.001**
1 Cortices	2(20.00)	1 (16.66)	1 (25)	
2 Cortices	1(10.00)	1 (16.66))	0 (0.00)	
3 Cortices	2(20.00	2 (33.33)	0 (0.00)	
4 Cortices	0 (0.00)	0 (0.00)	0 (0.00)	

** p<0.01, * p<0.05

There was also a significant difference between the groups for this variable at 18 weeks (p=0.001), although none of the participants had a fourth cortex observed. The intervention group participants had more cortices formed (n=4; 66.66 %) than those in the control group (n=1; 25 %). In the intervention group, more participants had two and three cortices bridged.

Fracture gap

The fracture gap presence was measured at the three time points and the difference between the participants with non-union fractures in the intervention and control groups is shown in Table 5.10. At six, 12 and 18 weeks significantly less participants in the intervention group had a fracture gap than in the control group (p= 0.000, 0.009 and 0.001) respectively. The fracture gap was still clearly visible for 100% participants with non-union fracture in the control group at six weeks, 80% (4) at 12 weeks and 75% at 18 weeks.

Table 5.10: The presence of a fracture gap in participants with non-union fractures in the intervention and control groups (n=12)

	Total n (%)	Intervention n (%)	Control n (%)	Fischer's exact (p-value)
Six weeks				
Observed	12 (100.00)	6 (100.00)	6 (100.00)	
Gap	9 (75.00)	3 (50.00)	6 (100.85)	0.000**
No Gap	3 (25.00)	3 (50.00)	0 (0.00)	
12 weeks				
Observed	11 (100.00)	6 (100.00)	5 (100.00)	
Gap	6 (80.70)	3 (50.00)	4(80.00)	0.009**
No Gap	5 (19.30)	3 (50.00)	1 (20.00)	
18 weeks				
Observed	10 (100.00)	6 (100.00)	4 (100.00)	
Gap	10 (100)	2 (32.43)	3 (75)	0.001**
No Gap	0 (0.00)	4 (67.57)	1 (25)	

** p<0.01, * p<0.05

5.3.3.2.2 Summary

When the results for participants with non-union fractures were considered, there was a significant difference between the intervention and control group for callus formation at 12 weeks. The intervention group had significantly more cortices bridged at 12 and 18 weeks indicating possible acceleration in fracture healing. The intervention group also showed a significant reduction in the fracture gap at six, 12 and 18 weeks, which may have assisted contact healing. The results for participants with non-union fractures represent a very small sample.

5.3.3.3 Within group change related to fracture healing over time.

The change in fracture healing within the intervention and control group was compared using the McNemar Chi-square test. The comparison was done at six, 12 and 18 weeks and the results indicate a positive change in terms of callus formation, cortices bridged, no fracture gap and overall healing within both groups. Some participants had loss of indicators of healing during the study indicating deterioration in fracture healing with loss of callus formation and cortical bridging and reappearance of the fracture gap due to complications.

5.3.3.3.1 Callus formation

Table 5.11 indicates the within group change for the presence or absence of callus within the different assessment periods for the intervention and control groups using per protocol analysis.

The results of the McNemar's test for within group changes showed that the intervention had a clinical effect over a period of six to 12 weeks. Over the six-week period there was no significant difference in callus formation with five more participants achieving callus formation. Since the majority of the intervention group already had callus formation by six weeks, there was an odds ratio of zero indicating no chance of deterioration and loss of callus formation. The change in callus formation in the control group was statistically significant (p=0.021) as a significant number of participants (n=9) in this group achieved callus formation between six and 12-weeks. One participant had deterioration in fracture healing during this period, with an odds ratio indicating a chance of 0.11 (CI- 0–0.80) for loss of callus formation possibly due to infection or further surgery in the control group.

In the 12-18-week period, fewer participants (three and five participants in the intervention and control groups respectively) moved from no callus, to callus formation, and the difference within both groups was not statistically significant. The odds ratio for both groups was zero, indicating no chance of deterioration and loss of callus formation. A similar result was seen when the results from six to 18 weeks were considered, with statistical significance for the intervention and control groups over this period as eight and 14 participants, respectively, having achieved callus formation.

Table 5.11. The within-group changes in callus formation for the intervention and control groups

Weeks	Group	No callus formed to callus formation	Callus formation to no callus formed	Odd ratio (CI=95 %)	p-value
Six – 12	Intervention	5	0	0 (0-1.09)	0.062
	Control	9	1	0.11 (0–0.80)	0.021*
12 – 18	Intervention	3	0	0 (0 – 2.42)	0.250
	Control	5	0	0 (0 – 1.09)	0.062
Six – 18	Intervention	8	0	0 (0 – 0.58)	0.007**
	Control	14	0	0 (0 – 0.30)	0.000**

** p<0.01, * p<0.05

5.3.3.3.2 Cortices bridged

To investigate the effect of LIPUS in the treatment of lower limb fractures, the McNemar Chi-square test for within group changes in cortices bridged are shown in Table 5.12. Between six and 12 weeks, the change in cortices bridged was significant for both the intervention and control groups (p<0.01). The odds ratio of zero indicated no chance that cortical bridging would be lost in either group. Twelve participants in the intervention group and 17 in the control group moved to cortical bridging in the period.

A 12-18 weeks, odds ratio for change from cortices bridged to no cortices bridged was higher at six (CI= 0.72 - 275.98), indicating some loss of cortical bridging in this period in the control group. The intervention group had a lower odds ratio of 0.25 (CI=0–2.53), with a much lower chance that cortical bridging may be lost and show as no cortical bridging during this period (one participant). Neither group showed statistical significance, as only four participants in the intervention group and one participant in the control group changed from no cortices bridged to cortical bridging.

Table 5.12. The change in the number of cortices bridged for the intervention and control groups

Weeks	Group	No cortices bridged to cortices bridged	Cortices bridged to no cortices bridged	Odds Ratio (CI=95 %)	p-value
Six – 12					
	Intervention	12	0	0 (0 - 0.35)	0.000**
	Control	17	0	0 (0 - 0.24)	0.000**
12 – 18					
	Intervention	4	1	0.25 (0–2.53)	0.380
	Control	1	6	6 (0.72–275.98)	0.130
Six – 18					
	Intervention	11	0	0 (0 – 0.39)	0.001**
	Control	9	0	0 (0 - 0.50)	0.003**

** $p<0.01$, * $p<0.05$

Significance was observed within both groups from six to 18 weeks for the change in the number of cortices bridged (11 and nine participants respectively) with an odds ratio of zero indicating no chance that participants would have lost any cortices bridged.

5.3.3.3.3 Fracture gap

The presence of a fracture gap was assessed using the McNemar's Chi-square test for both the intervention and control groups, between six and 12, 12 and 18 and six and 18 weeks, and presented in Table 5.13. Since the participants were scored as "yes" for having a negative adverse condition (a fracture gap) or "no" for a positive desired condition (no fracture gap), the confidence intervals in this case move towards zero.

The results for the analysis showed that the change in the presence of a fracture gap to no fracture gap in the intervention (p=0.002) and control (p=0.003) groups between six to 12 weeks was statistically significant. The participants in the intervention group and nine in the control group had their fracture gap closed in this period. The odds ratio of zero indicates no chance of a fracture gap reappearing in participants who had no fracture gap.

Table 5.13 the change in the presence of a fracture gap within weeks for the intervention and control groups

Weeks	Group	No fracture gap to fracture gap	Fracture gap to no fracture gap	Odd ratio (CI=95 %)	p-value
Six – 12					
	Intervention	0	10	0 (2.24-0)	0.002**
	Control	0	9	0 (1.97 – 0)	0.003**
12 – 18					
	Intervention	3	1	0.33 (0 – 4.15)	0.625
	Control	4	2	0.5 (0.04–3.49)	0.688
Six – 18					
	Intervention	0	5	0 (0.92 – 0)	0.063
	Control	0	3	0 (0.41 – 0)	0.250

** p<0.01, * p<0.05

Three participants in the intervention group who had no fracture gap presented with a fracture gap in the 12-18 week period, so there was a 0.33 (CI=0 – 4.15) chance that a fracture gap may reoccur. In the control group, four participants who had no fracture gap presented with a fracture gap resulting in a chance of 0.5 (CI= 0.04–3.49) for recurrence of a fracture gap during this period. No statistically significant change was found for either group between 12 and 18 weeks.

Overall, from six to 18 weeks the results for both groups were similar with an odds ratio of zero indicating no chance of recurrence of the fracture gap. The results showed that more intervention group participants had a resolution of their fracture gap.

5.3.3.3.4 Overall Healing

Table 5.14 shows the change in overall healing in the different periods within the intervention group and control groups. There was no statically significant change at any time period in either group for overall healing as only a few of the participants, who's X-rays were available at 12 and 18 weeks, had overall fracture healing. There was little change in the overall healing in the period six to 12 weeks with no statistical significance and odds ratio of zero at all time periods, with one participant in the intervention group and two in the control group achieving overall healing of their fractures.

Table 5.14 the change in overall healing within the intervention and control groups

Weeks	Group	No overall healing to overall healing	Overall healing to no overall healing	Odd ratio (CI=95 %)	p-value
Six –12					
	Intervention	1	0	0 (0 - 39.00)	0.317
	Control	2	0	0 (0 5 -0 32))	0.157
12 – 18					
	Intervention	1	0	0 (0.25-0)	0.317
	Control	1	1	1.00 (0.12 -.78.49)	1.00
Six – 18					
	Intervention	0	0	0 (0 – 0)	
	Control	0	0	0 (0 - 0)	

At 12-18 weeks, the change in overall healing remained the same, with odds ratio of zero for the intervention group as one participant had overall healing. In the control group the odds indicated a chance of one (0.12 -78.49) that healing seen may deteriorate and not heal.

No change was seen in overall fracture healing from six -18 weeks in either group.

5.3.3.3.5 Summary

The formation in callus and bringing of cortices from six-12 week was lower in the intervention group as they had already achieved these milestones in healing by six weeks. More participants in the control group achieved this healing after six weeks than by 12-weeks. One participant did lose callus during this period in the control group, indicating possible chance of deterioration for participants who received sham LIPUS. All participants achieved significant callus formation over the 18-week period of the study.

Changes for cortices bridged and no fracture gap were found for both groups in the six-12-week period indicating fracture healing related to these variables was significant in the intervention and control group groups. Odds ratios indicated a small chance for deterioration for cortices bridged, fracture gap and overall healing for the control group over the 12-18-week period. Only a chance of deterioration for cortices bridged was found for the intervention group

Over the six-18 weeks' study period, there was no change of deterioration for any variables related to fracture healing in both groups and significant change within the intervention and control group, except for overall healing of the fractures. Overall fracture healing did not occur except for four participants in the 18-week period, so the effect of LIPUS could only be determined on variables indicating healing and not overall healing (Buza III and Einhorn, 2016).

5.3.4 Influence of demographic, medical comorbidities and health status variables on fracture healing.

Logistic regression analysis was used to determine the influence of demographic, medical and health status variables on fracture healing. A univariate and multivariate logistic regression was done to identify all the variables that have influence on callus formation, bridging of cortices, and reduction of the fracture gap and overall healing of the lower limb fractures. These results are based on binomial values and the confidence intervals cannot span a null value, which can be considered to show significance. Since confidence intervals may still indicate significant association between two variables, the p-value was also considered to determine the significance of the association between variables.

The data for the logistic regression included the four variables used in the study to indicate fracture healing, callus formation, cortices bridged, presence of a fracture gap and overall healing, as dependent variables. The independent variables were the demographic, medical comorbidities and health status variables assessed in the participants and which literature indicates are associated with fracture healing (Neumann et al., 2016; Uusi-Rasi et al., 2019; Wang et al., 2017; Werfalli et al., 2018).

Due to the limited sample size in relation to the number of variables, univariate analysis was done for all variables, namely demographic, medical comorbidities and health status. Each was tested separately against all the dependent variables to minimise bias. A multivariate analysis was completed to provide predictive models of the association between fracture healing and demographic, medical comorbidities and health status variables (Sperandei, 2014). The data were checked to determine if there were no existing significant correlations between the independent variables.

Odds ratios greater than one, were interpreted as a positive relationship between the variable in question and fracture healing, whereas odds ratios below one were interpreted as a negative relationship and indicated a higher risk of no fracture healing associated with that variable.

5.3.4.1 Univariate analysis

The univariate analysis was completed for fracture healing, including all results for participants at six, 12 and 18 weeks. The demographic, medical and health status factors were analysed according to callus formation, cortices bridged, fracture gap and overall healing.

5.3.4.1.1 Callus formation

The factors associated with callus formation which were statistically significant, were gender type of fracture, type of management, fracture non-union and HIV status. In the univariate analysis in Table 5.15 for demographics and medical variables, females were 71% less likely to have callus formation with an odds ratio of 0.29 (CI=0.11-0.73). The analysis also indicated that the participants with tibia/fibular fractures were 50% less likely to have callus formation than those with femur fractures, and participants who were managed with ORIF were 67% less likely to have callus formation when compared to those who were managed with external fixation (Table 5.15).

No health status variables were associated significantly with callus formation when single variables were considered, except non-union, which was associated with the rate of callus formation in lower limb fractures with an odds ratio of 0.26 indicating those with non-union fractures were 74% more likely not to have callus formation six months or more post fracture.

Table 5.15 Univariate analysis model- The association between demographic and health variables and callus formation, cortices bridged, fracture gap and overall healing.

	Callus formation		Cortices bridged		Fracture Gap		Overall healing	
	Odds Ratio (CI=95 %)	**p-value**	**Odds Ratio (CI=95 %)**	**p-value**	**Odds Ratio (CI=95 %)**	**p-value**	**Odds Ratio (CI=95 %)**	**pvalue**
Gender -Male – Female	0.29 (0.11-0.73)	0.009**	0.42 (0.20-0.86)	0.024*	1.49 (0.75-2.96)	0.283	2.14 (0.23-19.30)	0.498
Age	1.00 (0.98-1.03)	0.480	1.00 (0.98-1.02)	0.823	0.98 (96-1.00)	0.204	0.95 (0.89-1.02)	0.217
Fracture site Femur- Tibia	0.52 (0.22–1.22)	0.139	0.89 (0.40-1.98)	0.781	0.84 (0.37-1.86)	0.682	0.86 (0.08-8.25)	0.897
Femur - Tibia/Fibula	0.50 (0.19-1.36)	0.171*	0.72 (0.29-1.82)	0.497	0.74 (0.30-1.83)	0.521	1.22 (0.12-12.34)	0.862
Fracture management External-Fixation – ORIF	0.37 (0.17-0.83)	0.016*	0.53 (0.25-1.12)	0.005**	1.24 (0.60-2.58)	0.540	1.34 (0.22-7.83)	0.745
Smoker	0.60 (0.28-1.30)	0.191	0.66 (0.34-1.30)	0.261	1.82 (0.93-3.52)	0.079	0.26 (0.04-1.52)	0.136
HIV positive	1.30 (0.63-2.74)	0.474	1.21 (0.63-2.31)	0.553	0.69 (0.36-1.31)	0.250	0.61 (0.10-3.54)	0.582
Cancer	1.00	1.00	1.00	1.000	0.32 (0.04-2.22)	0.251	0.77 (0.08-7.00)	0.817
Not-union of fracture	0.26 (0.10-0.65)	0.004**	0.42 (0.20-0.86)	0.024*	0.88 (0.39-1.99)	0.771	1.00	1.000
Diabetic	1.14 (0.48-2.66)	0.755	1.00 (0.98-1.02)	0.823	1.20 (0.56-2.56)	0.614	1.00	1.000
Hypertensive	1.60 (0.65-3.89)	0.301	0.89 (0.40-1.98)	0.781	0.72 (0.33-1.54)	0.432	2.14 (0.23-19.30)	0.498

*** p<0.01, ** p<0.05 *

5.3.4.1.2 Cortices Bridged

The univariate analysis in Table 5.16 for demographic and medical factors indicates similar results to those found for callus formation for gender and fracture management. Females are at 58% less likely to have cortices bridged, with an odds ratio of 0.42 (0.200.86). The analysis also indicated that the participants who were managed with ORIF were 47% less likely to have cortices bridged compared to those managed with external fixation (Table 5.15).

No health status variables were significantly associated with callus formation when single variables were considered.

5.3.4.1.3 Fracture Gap

The univariate analysis in Table 5.15 for demographics, medical comorbidities and health status variables indicated no association between any variables and the presence of a fracture gap. The odds ratios are inverted, as a positive outcome for fracture gap was present where fracture gap was absent.

5.3.4.1.4 Overall healing

The interaction of the univariate logistic analysis of lower limb fracture overall healing, demographic medical comorbidities and health status factors showed no significant associations (Table 5.15).

5.3.4.2 Multivariate analysis

5.3.4.2.1 Time Frame

The healing of the fractures over time at six weeks, 12 weeks and 18 weeks was analysed to determine the association of related to callus formation, cortices bridged, fracture gap and overall healing. The analysis used the healing in the control group as a reference against which to develop a multivariate model and predict the odds for healing at over 12 and 18 weeks in the control group, as well as healing that occurred at all three timeframes in the intervention group in relation to the control group at six weeks.

Callus formation

The multivariate logistic regression at 12 weeks showed a significant interaction between time and the control group (p=0.049) analysis with odds ratio of three (CI=1.00-9.19), indicating a high likelihood of callus formation at this time.

One hundred and twenty-two participants in both the intervention and control groups had higher odds of callus formation at 12 weeks in a regression model associated with the demographic and health related fractures (Table 5.16).

This logistic regression model indicated that participants in the control group were three times more likely to have callus formation at 12 weeks than at six weeks, while those in the intervention group were six times more likely to have callus formation at 12 weeks than that recorded for the control group at six weeks. However, while the participants in the control group had an odds ratio of one at 18 weeks, indicating similar callus formation as that seen at six weeks, the participants in the intervention group were 32 times more likely to have callus formation at 18 weeks compared to the control group at six weeks.

Cortices bridged

When modelling a multivariate analysis considered for the period six to 18 weeks using cortices bridged at six weeks in the control group as a reference, participants in both the intervention and control groups had higher odds of cortices bridged at 12 weeks. This logistic regression model indicated participants in the control group were 13 times more likely to have cortices bridged at 12 weeks than at six weeks, while those in the intervention group were only seven times more likely to have cortices bridged at 12 weeks. However, while the participants in the control group had an odds ratio of 4 at 18 weeks, indicating they were four times more likely to have cortices bridged than at six weeks, the participants in the intervention group were 10 times more likely to have callus formation at 18 weeks compared to the control group at six weeks.

Table 5.16 Multivariate analysis: The association between timeframe in weeks for healing and callus formation, cortices bridged, fracture gap and overall healing.

	Callus formation		Cortices bridged		Fracture Gap		Overall healing	
	Odds Ratio (CI=95 %)	**p-value**	**Odds Ratio (CI=95 %)**	**p-value**	**Odds Ratio (CI=95 %)**	**p-value**	**Odds Ratio (CI=95 %)**	**p-value**
Control group – six weeks	1.00	1.000	1.00	1.000	1.00	1.000	1.00	1.000
Control group – 12 weeks	3.03 (1.00-9.19)	0.049*	13.15 (4.22-40.95)	0.000**	0.20 (0.11-2.89)	0.004**	2.61 (0.15-44.72)	0.507
Control group – 18 weeks	1.00	1.00	4.17 (1.35-12.88)	0.013**	0.32 (0.19-0.43)	0.055*	2.32 (0.08-65.51)	0.621
Intervention group –six weeks	2.16 (0.79-5.87)	0.131	0.81 (0.02-2.34)	0.705	1.28 (0.73-1.92)	0.665	1.00	1.000
Intervention group –12 weeks	6.47 (1.60-26.12)	0.009**	7.06 (2.97-38.62)	0.001**	0.15 (0.09-3.23)	0.001**	2.00 (0.13-29. 13)	0.612
Intervention group –18 weeks	31.95 (3.25-313.34)	0.003**	10.71 (0.85-1188.28)	0.000**	0.24 (0.15-2.26)	0.024**	1.00	1.000

*** p<0.01, ** p<0.05 *

Fracture gap

When modelling a multivariate analysis for the time-frame six to 18 weeks using fracture gap at six weeks in the control group as a reference, there was significant interaction for time with odds ratio of 0.15 (0.09-3.23) and an odds value ratio of 0.24 (0.15 – 2.26) at 18 weeks (Table 5.16). In both groups, the likelihood of no fracture gap increased over time. Participants in both the intervention and control group had negative association with the presence of a fracture gap, indicating more likely to have no fracture gap at 12 weeks in a regression model. This logistic regression model indicated participants in the control group were 80% less likely to present with a fracture gap while those in the intervention group were 95% less likely to have a fracture gap at 12 weeks. However, while the participants in the control group were 68% less likely to present with a fracture gap at 18 weeks, the participants in the intervention group were 76% less likely to present with a fracture gap compared to those at six weeks in the control group.

Overall healing

When modelling a multivariate analysis for the timeframe over six to 18 weeks, using overall healing at six weeks in the control group as a reference, no significant interaction for time was found for the control group at 12 and 18 weeks and intervention group at six, 12 and 18 weeks (Table 5.16). It can be assumed that this analysis reflects the reported lack of overall fracture healing by 18 weeks in the current study.

5.3.4.2.2 Demographic medical comorbidities and health status factors

When modelling a multivariate analysis, which included the demographic medical comorbidities and health status factors, the variables were considered for the timeframe over six to 18 weeks using callus formation at six weeks in the control group as a reference.

Callus formation

In the multivariate analysis, only the demographic factor of gender was predictive of callus formation and indicated females were still 71% less likely to have callus formation. Only non-union, in the health-related factors, was associated with the rate of callus formation in this model, with 77% of those with non-union fractures more likely not to have callus formation 6 months or more post fracture (Table 5.17).

Table 5.17 Multivariate analysis model: The association between demographic and health variables and callus formation.

	Callus formation		Cortices bridged		Fracture Gap		Overall healing	
	Odds Ratio (CI=95 %)	**p-value**	**Odds Ratio (CI=95 %)**	**p-value**	**Odds Ratio (CI=95 %)**	**p-value**	**Odds Ratio (CI=95 %)**	**p-value**
Gender -Male – Female	0.29 (0.11-0.74)	0.023*	0.42 (0.18-.96)	0.041*	1.40 (0.62-3.17)	0.416	1.19 (0.08-15.96)	0.892
Age	0.99 (0.98-1.03)	0.623	0.98 (0.95-1.02)	0.453	0.97 (0.94-1.00)	0.134	1.03 (0.91-1.15)	0.624
Fracture site Femur- Tibia	0.86 (0.22-1.22)	0.788	1.53 (0.54-4.28)	0.415	0.67 (0.24-1.88)	0.454	0.28 (0.01-6.56)	
Femur - Tibia and Fibula	0.62 (0.19-1.36)	0.436	0.91 (0.31-2.62)	0.863	0.58 (0.20-1.63)	0.303	0.53 (0.03-7.88)	0.648
Fracture management External-Fixation –ORIF	0.61 (0.16-0.82)	0.373	0.61 (0.22-1.69)	0.344	2.04 (0.74-5.59)	0.165	3.01 (0.20-45.12)	0.425
Smoker	1.03 (0.28-1.30)	0.939	1.02 (0.47-2.21)	0.954	1.96 (0.91-4.19)	0.083	0.34 (0.04-2.36)	0.277
HIV positive	2.26 (0.63-2.70)	0.069	1.89 (0.90-3.95)	0.089	0.47 (0.22-.98)	0.046*	0.24.02-2.41)	0.228
Cancer	1.00	1.000	1.00	1.000	0.55 (0.04-6.17)	0.628	0.82 (0.05-12.22)	0.892
Not-union of fracture	0.23 (0.10-0.64)	0.024*	0.43 (0.13-1.38)	0.159	0.66 (0.22-1.94)	0.451	1.00	1.000
Diabetic	0.36 (0.I47-2.63)	0.172	0.55 (0.16-1.82)	0.331	2.14 (0.66-6.89)	0.198	1.00	1.000
Hypertensive	3.04 (0.63-3.89)	0.108	1.70 (0.53-5.42)	0.364	0.69 (0.22-2.11)	0.522	1.19 (0.08-15.96)	0.892

*** p<0.01, ** p<0.05 *

Cortices bridged

In the multivariate analysis, only the demographic factor of gender was predictive of cortices bridged and indicated females were still 58% less likely to have cortices bridged. No other factors showed significance in the multivariate logistic regression.

Fracture gap

In the multivariate analysis, only the health comorbidity factor of HIV was predictive of fracture gap and indicated participants who were HIV positive were still 53% less likely to have no fracture gap. No other factors showed significance in the logistic regression.

Overall healing

The multivariate interaction in the logistic analysis of lower limb fracture overall healing and demographic medical comorbidities and health status factors showed no significant associations (Table 5.17).

5.3.4.3 Summary

The influence of demographic, health status variables and smoking on fracture healing, when all factors affecting fracture healing were considered, compared to the callus formation, cortices bridged and presence of a fracture gap in participants in the control group at six weeks. Participants in the control group were more likely to have cortices bridged and callus formation at 12 weeks, and the absence of fracture gaps at 18 weeks. The intervention group was more likely to have callus formation, cortices bridged and absence of fracture gaps at 12 and 18 weeks. Female participants were less likely to have callus formation and cortices bridged than males in univariate and multivariate analysis.

- Participants with ORIF were likely to have less callus formation in univariate and multivariate analysis, and fewer cortices bridged in univariate analysis.
- Participants diagnosed with non-union were likely to have less callus formation in univariate and multivariate analysis.
- All HIV positive participants were more likely to a fracture gap when considered in the multivariate analysis.

5.4 DISCUSSION

The discussion considers the results of Phase 2 of the study including the participants' demographics, fracture healing and the association of demographic, medical and health status with fracture healing.

5.4.1 Demographics and Health Status of the Study Sample

5.4.1.1 Age and Gender

The demographic characteristics results in the present study show there were more males (67.8%; n=78) with lower limb fractures than females (32.17%; n=37). This is in agreement with a study in Brazil, which found that males have a higher prevalence of lower limb fractures than females (Oliveira et al., 2018). This is due to males being exposed to a more active lifestyle and being involved in activities with higher risk for injury and fracture in sports and work-time outside home. Traffic accidents play a role for both males and females, while females are more likely to suffer lower limb fractures in the home due to falls (de Andrade Rodrigues et al., 2012).

The mean age of females with fractures was 48.86 (SD 18.33) years compared to 38.54 (SD 13.18) years for males. The mean age correlates with an epidemiological study in England, which found that older females reported more incidences of fractures (Scholes et al., 2014) and that lower limb fractures were more common in younger males of 30 to 39 years (Kaye and Jick, 2004). Since fracture prevalence only rises in older females at 55 years due to the development of osteoporosis (Vanhaecht et al., 2012), this factor did not play a role in the current study. There was no significant difference in the age of the participants in the intervention and control groups, with both groups having a mean age in the 40s and a similar distribution of fracture sites.

As reported by the literature, the greatest percentage of fractures (60%) occurred in the femur. Tibia fractures were second highest in prevalence, with a frequency of 13.48% (24) and tibia/fibula fractures were the least prevalent. This was contrary to the literature, which reported a higher incidence of ankle and tibial fractures (de Andrade Rodrigues et al., 2012; Kaye and Jick, 2004). The difference in the current study may be due to only surgically managed fractures being included as the selection criterion. No studies indicating incidence of fractures sites surgically managed in South Africa were available, which may to some extent account for the lack of ankle fractures and limited tibia, tibia/fibula fractures in the current study.

5.4.1.2 Health Status

Non-union fractures were found in 14.78% of this study sample, which included comminuted fractures. These results are in line with the report of between 8 and 20% in a study classifying non-union fractures (Calori et al., 2007), though higher than the 5 to 10 % suggested by Romano et al. (2008), with no figures available for South Africa. Thus, the percentage of participants presenting with non-union fractures was lower than that reported in the literature, even though other comorbidities had a much higher prevalence than other studies reporting on fracture healing and LIPUS.

Fractures are complex to treat and the causes of non-union vary from patient to patient. Research has found that smoking and the presence of comorbidities such as HIV and diabetes have been found to have a significant contribution to the prevalence of non-union fractures (Abate et al., 2013; Al-Hadithy et al., 2012; Graves et al., 2011). In this study, the prevalence of non-union is likely because of a combination of factors that include smoking, and HIV, hypertension and diabetes.

The current study found that the comorbidity with the highest prevalence at 43.5 % of the participants was HIV. In patients with HIV, the likelihood of fractures is higher due to the prevalence of low bone mineral density (BMD) (McComsey et al., 2010b). With such underlying mechanisms, such as complex interactions between the HIV infection, traditional osteoporosis risk factors and the antiretroviral therapy (ART) influencing bone mineral density in individuals with HIV infection appears to be multifactorial (McComsey et al., 2010b). There is a significantly higher prevalence of fractures in individuals with HIV at 2.87 per 100 compared 1.77 per 100 in HIV negative individuals (Martin et al., 2013).

In this study, 60.8% of the participants smoked, while participants with hypertension and diabetes had a high prevalence in this study at 25.22% and 26.96% respectively. Comorbidities such as diabetes and hypertension have been increasing in South Africa and the prevalence of diabetes has been rising globally since the 1980s. The prevalence of hypertension is in line with other low and middle-income countries (LMICs) at 32%, but in this study the prevalence of patients with diabetes was higher by 7% in adults from other LMIC (Morris-Paxton et al., 2018). Patients with these comorbidities have a higher risk for fractures. Ye et al. (2017), in their meta-analysis, found a relationship between bone density, blood pressure and serum osteocalcin. The bone density of hypertensive patients was significantly lower than expected and antihypertensive drugs have also been associated with cancellous bone loss, although further research is needed to confirm these results (Ye et al., 2017).

5.4.2 Fracture healing

The first objective of this phase of the study was to determine the difference in fracture healing in lower limb fractures for participants managed surgically and with LIPUS compared to the participants managed only surgically. The research sought to understand how LIPUS could be best applied in accelerating bone healing.

Fractures disrupt and compromise a patient's quality of life when they experience pain, limitation in physical function and reduced productivity through inability to work (Kerr et al., 2017). Lower limb fractures, in particular, can be quite devastating due to reduced mobility, which often means a need for a caregiver to assist in activities of daily living. Prolonged absence from work by the patient may eventually lead to loss of wages, negatively impacting on the household income (Cancelliere et al., 2016). Not only are fractures a burden on the patients and their families, they are also associated with high costs for state hospitals (Xie et al., 2015).

The outcome on the effect of LIPUS on fracture healing must be viewed in light of the large loss to follow up in this study. At 18 weeks, it is possible that some participants did not return as they had a good outcome and their fractures had healed or nearly healed, or the treating doctor did not see the reason to return the patient for a follow-up or take further X-rays. Thus, the loss to follow up may not have been entirely random.

These results may reflect that for participants who remained in the study and returned in the later weeks, fracture healing was slow or delayed. This is confirmed by the higher percentage of participants who presented with signs of incomplete healing at 12 and 18 weeks. Although the percentage was low, 10 out of 44 participants (22.7%) who remained at 18 weeks presented with non-union fractures compared to 14.7% at the start of the study. This delayed healing and non-union fractures may have been related to fracture complications, such as the development of infections normally treated by antibiotics, (Traeger et al., 2014) and the fact that only surgically managed fractures were considered in the current study. The type of fracture management may have added to the overall risk of non-union, which is increased by surgical intervention (Ferreira et al., 2016a). Since external and internal fracture fixation were used to treat all the lower limb fractures in the current study, the fractures may have been unstable and prone to non-union, although non-union can be exacerbated if they are fixed too rigidly (Perumal and Roberts, 2007). Fracture site may also have played a role since blood supply in tibial fractures with associated soft tissue damage is typically disrupted when they are managed with open reduction and internal fixation (Ferreira et al., 2016a).

Since this study was focused on lower limb fractures, which are the primarily weight-bearing bones responsible for mobility in a patient, the fractures are therefore prone to disruption. The fractures may be disrupted if patients attempt to bear weight or walk without external support too soon, leading to a slower rate of healing. Delayed healing in the participants may also have been associated with the patient demographic comorbidities and health risk factors.

The lack of fracture healing was found to be low for both the control and intervention groups due loss to follow up in both groups, which was similar, and presented as little difference between the groups at 18 weeks.

5.4.2.1 Comparison of fracture healing in the intervention and control groups

The first variable to support fracture healing considered in the study was callus formation. The results found in this study reflect those reported in the literature. At six weeks, 72.09% of participants in the intervention group and 57.45% of patients in the control group had callus formation. This supports clinical studies, which indicated accelerated callus formation in patients who received LIPUS, and that LIPUS can enhance and stimulate healing of fresh fractures and surgically treated fractures (Valderrábano and Linares, 2018; Richardson et al., 2008). In the current study, 15% of the participants in the intervention group had callus formation 42 days earlier than in the control group. Other studies on surgically managed fractures supported these findings, where healing was accelerated by between 20 and 60 days (Leung et al., 2004; Nolte et al., 2009; Emami et al., 1999), although this was not statistically significant. Thus for some participants, the accelerated callus formation could reduce healing time.

There were similarities between the results of the current study and the study by Cheung et al. (2011), which also showed a lower percentage of participants in the control group had callus formation in the first six weeks. However, these two studies differed in that in this study, callus formation continued up to 18 weeks although in smaller percentages of participants, whereas Cheung et al. (2011) found a significant decrease in callus formation at eight weeks of exposure to LIPUS.

Although in the current study at 12 weeks the percentage of the participants in the intervention group who had callus formation was less than in the control group, 7.2% of participants still achieved callus formation during this period. At 18 weeks, all the participants in both groups had callus formation, except for one participant in the intervention group (Table 5.4). Using the Pearson’s Chi-square test, the differences between the groups for callus formation were not statistically significant. The results of the current study confirm low evidence from other high-quality studies (Busse et al., 2002; Jingushi et al., 2007; Rutten et al., 2012) that LIPUS therapy may accelerate callus formation and thus fracture healing in lower limb fractures, although the difference does not reach significance within the first three months (Kinami et al., 2013a).

The greater increase in callus formation seen in the first six weeks in the intervention group may be due to LIPUS stimulating new blood vessels in the initial phase of exposure during the inflammatory stage of fracture healing, increasing angiogenesis and accelerating the reparative and callus remodelling in the early weeks of healing (Cheung et al., 2011). Other authors only report acceleration of callus formation in surgically managed fractures from with no LIPUS eight weeks’ post-fracture (Leung et al., 2004), as was found in the current study.

In the participants who presented with non-union, there was no difference in the intervention and control group at six weeks but by 12 weeks, the intervention group had greater callus formation. This confirms that LIPUS may accelerate callus formation, but when non-union is present this takes longer to initiate as LIPUS does not initiate fracture healing. By 18 weeks all the participants in both the intervention and control group had callus formation indicating these participants probably had hypertrophic non-union, which shows prolific callus formation and can be considered as having the potential to heal (Watanabe et al., 2010).

The second variable considered, concerning fracture healing, was cortical bridging. Cortical bridging of three or more cortices is considered radiological healing (Goldhahn et al., 2008). The results of cortices bridged, calculated using Pearson's Chi-square at six, 12 and 18 weeks, showed no significant difference between the intervention and control group. The results showed a steady increase of up to three cortices bridged from both the intervention and control groups, with no significant difference in the percentage of participants with no cortex bridged at six weeks, although a greater percentage of the control group had no cortices bridged.

In the current study, the highest number of cortices bridged were observed after 12 weeks, which concurs with the results of a study in Japan, which found there was faster bone growth with radiographic bridging at the fracture site after three months (Koga et al., 2013). However, at this stage, a lower percentage of participants in the intervention group had cortices bridged than the control group. Again, this confirms that although healing may have been accelerated in the intervention group, the control group achieved similar healing by 12 weeks. These results correlate with the findings of Cheung et al. (2011), which showed cortical bridging for the LIPUS treatment group at five to six weeks after fracture and for the control group at a later stage, between seven to eight weeks.

At 18 weeks, of the participants who returned at this stage and were X-rayed, a higher percentage of participants in both groups had not achieved cortical bridging compared to 12 weeks. This supports the assumption that participants with delayed fracture healing were returning at this stage. Although there was no significant difference between the groups, participants in the intervention group had more cortices bridged (Table 5.5), which indicated greater healing even for those with some delay in healing in the intervention group at this stage.

This finding was supported when the participants with non-union fracture were considered, and at 18 weeks, the participants in the intervention group had significantly more cortices bridged than did those in the control group. This is congruent with other studies, which indicated more effect of LIPUS in non-union fractures with healing in 80 days as opposed to more than 120 days for the control group (Rutten et al., 2012). This resulted in the participants with non-union fracture intervention group also having significantly more cortices bridged at 12 weeks, which was contrary to the findings for the total group of participants.

The third variable considered in relation to fracture healing was the reduction or absence of a fracture gap. The number of participants with a fracture gap decreased in both the intervention and control groups at six to 12 weeks and marginally increased at 18 weeks in the participants with delayed healing who returned at this stage for X-ray. There were no significant differences observed between groups using the Pearson's test. Although the percentage of participants in the intervention group with no fracture gap was lower than that of the control group at six weeks, the intervention group had a higher percentage of participants with no fracture gap at 12 weeks. Thus, although the participants in the intervention group had greater callus formation in the first six weeks this did not reduce the fracture gaps present until 12 weeks, which indicates that LIPUS had less effect on the closure of the fracture gap. This may have been related to the size of the fracture gaps, which were not recorded in the current study. Multivariate logistic analysis revealed that the risk for failure of union with LIPUS was increased when an 8 mm or more fracture gap size was present (Watanabe et al., 2010). This trend was confirmed, as at 18 weeks a higher percentage of participants in the control group presented with no fracture gap.

The reduction of fracture gaps was significantly better for the non-union fracture intervention group over six, 12 and 18 weeks when compared to the control group. This supports the findings of (Takikawa et al., 2001) that at four weeks, in patients who receive LIPUS exposure, the fracture gap shows both intramembranous and endochondral bone formation even though the fracture could be identified. As in this study, the control group did not show reduction of the fracture gap indicating that this variable in the healing of non-union fractures LIPUS is effective.

Finally, the overall healing of the fractures was assessed on the X-rays. The difference in overall healing for the intervention and control groups was calculated using Pearson' Chi-square test and the results established there was fracture healing only at the 18 week period for a small number of participants who were X-rayed at that time. There was no significant difference in overall healing rate between the intervention and control groups. The lack of significance is supported by another study, as the systematic review by Rutter et al. (2012) indicated that LIPUS favours fracture healing in patients managed surgically and that healing occurs within seven to 16 weeks compared to 11 to 23 weeks for patients who do not receive LIPUS.

This is discordant with the findings of other studies whose intervention group showed complete healing after 16 weeks of exposure to LIPUS (Koga et al., 2013). These findings may be related to the loss to follow up in this study, where it appears that participants who neither had nor achieved healing returned at 18 weeks and were X-rayed. The dose of LIPUS used in this study was also less than that reported in other studies as it was only applied every second day and this may have had an impact on the effectiveness.

The use of LIPUS in the South African context for patients with lower limb fractures appears to be restricted due to the limited access to the equipment and the need to provide treatment over a three to eight-week period. The use of LIPUS in fracture treatment is required daily, and needs to continue at home once the patient is discharged. Due to the resource constraints in terms of the equipment availability, it is not possible to provide them with a machine to use at home. Simultaneously, it will be costly for patients to travel daily to the hospital for LIPUS treatment daily considering some patients live far from the hospitals and rely on public transport. This further supports the finding that other than lack of effectiveness in promoting fracture healing, LIPUS may not be a technique to be considered in the South African public health sector.

When considering the group with non-union fractures, no overall healing was found for any of the participants in the intervention and control groups over the 18-week period as discussed above. This was expected, as non-union fractures take up to five months to heal (Dijkman et al., 2009a). The intervention group had significantly greater signs of healing with 68 to 100% of participants having consolidation in three variables used to determine healing. This healing was probably supported by the lack of infection, which was seen in the patients in Phase 1 Part 2 where healing did not occur in six months follow up.

This supports the conclusion of Leighton et al. (2017) that results are better in biologically active non-union fractures, which are not infected when LIPUS is applied within six months after the last surgical revision of the fracture. Given an overall average success rate for LIPUS for non-union fractures where healing has been found to be significantly better than that of controls, with 82% of femur and 84% of tibia fractures healing post application of LIPUS (Romano et al., 2009), this study continues to support the addition of LIPUS to surgical managed non-union fractures.

There was a higher prevalence of participants with health comorbidities in the group with non-union fracture. The participants had higher percentages (52.9%) who were HIV positive, 76.4% smoked and 23.5% had a prevalence of diabetes and hypertension. This further supports the use of LIPUS with non-union fracture in this population, as the results indicated that significant healing could be achieved in the presence of greater comorbidities. However, the very small sample for non-union fractures must be taken into account in relation to this conclusion.

5.4.2.2 Fracture healing within groups

Within the groups, differences for the intervention and control group were calculated to determine there were no detrimental effects of the use of LIPUS in surgically treated fractures. The McNemar's Chi-square test was used to analyse the differences within the intervention and control groups. Some studies have reported non-union after LIPUS treatment. The relative risk of impaired healing by LIPUS is 0.70 (95% CI, 0.31 to 1.58), with deterioration in healing reported in two studies for fresh fractures and in the upper limb (Busse et al., 2002; Emami et al., 1999).

When considering callus formation, the results showed a significant callus formation in the control group at six-12 weeks, whereas the intervention group already had a high percentage of callus formation before six weeks. While no participants in the intervention group showed deterioration in this period, one participant from the control showed deterioration with loss of callus.

Both groups showed no significant callus formation at 12-18 weeks, but callus formation was significant for both groups over the entire period from six to 18 weeks. Thus, the intervention group showed no detrimental effects of LIPUS on callus formation.

Cortical bridging was evaluated for both the intervention and control groups, and at this stage, participants in both groups had deterioration in the number of cortices bridged. However, the odds ratio for deterioration in the intervention group was much smaller at 0.25 compared to that of six for the control group. This confirms the likelihood of better cortex formation in the intervention group from 12 weeks. This indicates LIPUS may have a protective role in surgically managed fractures and participants were far less likely to have deterioration in cortical bridging in the 12-18-week period. Significant cortical bridging was seen in both groups in the six-18-week period.

Fracture healing results when a fracture gap closes. There was a significant closure of the fracture gap for both groups between 6-12 weeks, with neither group having any deterioration and return of a fracture gap. These results correspond to the study by Cheung et al. (2011), which found that bridging of the fractured gap occurred at four to six weeks in the group treated with LIPUS and a control group. There was no further significant closure of fracture gaps for both groups at 12-18 weeks. In this period participants in both the intervention and control group had deterioration and return of a fracture gap. However, the likelihood of deterioration in the intervention group was lower, with an odds ratio of 0.333 compared to 0.50 for the control group. Overall, between six18 weeks no significant change in the fracture gap was seen in both the intervention and control groups.

Overall healing did not achieve significance in either group at any period. One participant in the control group did have deterioration in overall healing in the 12-18 week period. The findings of within group analysis therefore indicate that LIPUS does not appear to have a detrimental effect on fracture healing compared to that recorded for the control group.

While the deterioration seen could have been due to infection of repeated surgery, the adherence of the participants also played a role. Some participants had missing X-rays at six weeks, but their X-rays at 12 weeks and 18 weeks were available. In these patients this could account for the deterioration seen at 12 weeks as their fractures may have had more delayed healing in relation to the fracture healing of other participants at six weeks.

5.4.3. Influence of demographic, medical and health status variables on fracture healing.

Logistic regression was used to determine the association of demographic, medical and health status variables with fracture healing. This was to confirm if similar variables predicted fracture healing as reported in the literature. The logistic regression was also used to establish the role of the higher prevalence of medical comorbidities in relation to fracture healing in the context of the current study (Westgeest et al., 2016). The logistic regression for single factors found fracture healing to be associated with gender, site of fracture management and non-union.

5.4.3.1 Demographics Factors

When considering demographics, gender showed a significant association to fracture healing in both the univariate and multivariate models. Female patients were less likely to have callus formation and cortices bridged. Westgeest et al. (2016), who reported similar findings, support these results. Gesicki, et al. (2003) also found that females were at risk of delay and non-union in fracture healing due to the influence of oestrogen.

Oestrogen has a significant impact on cortical width, cortical mineralisation and the amount of intramedullary callus resulting in decreased fracture healing in females. Oestrogen is a critical factor in fracture healing in women just as testosterone leads to fracture stability and healing in men (Gesicki et al., 2003).

5.4.3.2 Medical variables

When considering medical variables, including fracture site and fracture management showed a significant association to fracture healing in the univariate models for callus formation. Participants with tibia/fibula fractures were less likely to have callus formation than those with femur fracture. Literature indicates fracture site may result in different outcomes, and Westgeest et al. (2016) reported double the percentage of patients, from a cohort of 736 participants, presented with significantly delayed healing when they presented with a fracture of the tibia and fibula compared to those with fractured femurs. Their study supported the findings of the current study in that this variable was only found in a univariate analysis.

The results of the logistic regression univariate analysis showed there is a significant relationship between the fracture management and callus formation, with participants treated with ORIF less likely to have callus formation than those treated with external fixation. There was a similar finding for the association of cortices bridged and univariate analysis. Research indicates that fractures treated with external fixation were more likely to have callus formation and more cortices bridged, since ORIF tends to inhibit callus production while more callus production is seen when external fixation is used (Meng and Zhou, 2016). Reaming of the intramedullary canal for internal fixation interferes with endosteal blood supply and destroys the nutrient artery affecting callus formation (Brinker et al., 1999).

5.4.3.3 Comorbidities and health risk behaviour

The HIV positive participants had greater presence of a fracture gap on multivariate analysis, indicating slowed healing when considered in combination with other factors. This is similar to the study by Harrison (2009), who found that 33% of non-union patients were HIV positive. Possible causes of disturbed fracture healing among people with HIV is the reduced body mass index, suboptimal nutrition, and the effects of anti-retroviral drugs (Arnesen et al., 2003; Richardson et al., 2008). HIV and the altered inflammatory response of the immune-compromised patient (Harrison, 2009) may adversely affect fracture union. The imbalance between bone resorption and bone formation leads to loss of bone density, and an increased incidence of delayed healing and non-union (Richardson et al., 2008; Harrison, 2009). Apart from the directly impeding cellular function in bone remodelling, HIV infection is known to cause derangement in the levels of those cytokines involved in the fracture healing and appears to impair blood supply of the bone (Richardson et al., 2008). HIV infection can also complicate open fractures by raising the incidence of infection in the open wounds. The risk may be compounded if open reduction internal fixation techniques are used (Harrison, 2009).

Currently in South Africa, when people are diagnosed with HIV they are immediately placed on anti-retroviral therapy (ART) (Schwartsmann et al., 2015). Low BMD and osteoporosis can be three times greater in HIV infected people on ART (McComsey et al., 2010b). Thus, both chronic inflammation and possibly the virus itself affect bone resorption osteoclast activity. However, the underlying pathophysiology is unknown. It is possible that HIV-positive patients treated with ART experience a lower overall rate of ossification leading to slower fracture healing and delayed union (Richardson et al., 2008).

As in other studies, although there was a higher prevalence of comorbidities, diabetes, hypertension and smoking did not reflect as predictors of fracture healing in the regression model in the current study. This supports the findings of Watanabe et al. (2010), who also reported no effect of smoking on fracture healing and delayed healing in a LIPUS study.

A significant relationship between callus formation and fracture non-union in both the univariate and multivariate logistic progression was found. Callus formation occurs within one or two weeks after a fracture or injury, and consists of cartilaginous material, which connects across a bone fracture during the repair process (Marsell and Einhorn, 2011). When callus formation does not occur, it delays fracture healing and results in non-union if there is no callus formation at six months' post fracture. Therefore, this association was not unexpected, although no significant association was found for cortical bridging and fracture gap and non-union as expected as these also reflect fracture healing, which is absent in non-union.

5.4.4 Limitations of the study

5.4.4.1 Loss to Follow up

The over 50% loss to follow up during the research period was affected by the research setting in two tertiary hospitals in Gauteng Province. The research setting had an impact on the data collection for this study and affected the availability of X-rays required over the 18 weeks in which fracture healing was evaluated. In South Africa, state hospital services are divided into three levels, tertiary, secondary and primary care. This research was conducted in a tertiary hospital setting that deals with surgical and acute management of fractures.

In orthopaedics, tertiary hospitals have operating theatres. Most tertiary hospitals have enough resources to perform surgical management and have Intensive Care Units in the event of complications arising. X-rays are normally taken on admission for diagnostic purposes, post-operatively, and at each follow-up visit, which is normally booked at six, 12 and 18 weeks post discharge. Depending on the surgeon's opinion, patients may not be required to attend all three follow-up visits. Patients sometimes miss follow up appointments due to personal circumstances, and one or more of the recommended follow-up visits. This results in loss of X-ray data for any of the follow up weeks.

A patient who was medically stable may be transferred to a secondary or primary hospital where they continue with their follow-up observation and the prescribed or chronic medication. Therefore, future X-rays occur at the secondary hospital, but these were not available for participants in this study. Some patients who were admitted to the secondary hospital and developed complications were transferred back to the tertiary hospital for further management and X-rays were then available for these patients in the later follow up weeks. Patients with complicated fractures were routinely followed up at the tertiary hospital.

At the two tertiary hospitals where the research took place, Steve Biko Academic Hospital (SBAH) stored X-rays electronically, whereas Kalafong Hospital filmed the X-rays in hard copy and stored them on shelves. The patient's admission number in the patient record is the same as the X-ray number at SBAH, whereas it is different at Kalafong Hospital. While it was easy to trace missing X-rays at SBAH, if the patient's record was missing at Kalafong Hospital, tracing the X-ray number was difficult as the X-ray number is stored at the back of the patient record. In cases where a patient had the missing record replaced with a new one, which is very common at Kalafong Hospital, it is impossible to trace the X-ray number. Both hospitals are teaching hospitals therefore X-rays are used for diagnostic purposes and for teaching purposes. When records and X-rays have been removed for these purposes the Chief Executive Officer of the particular hospital and the department that has the record or X-rays need to be approached and a formal request for the documentation made. This resulted in loss to follow up over the 18-week period of X-rays for participants. Every effort was made to follow up missing X-rays for the patients at both hospitals by the primary researcher.

5.4.4.2 Radiographic measurements

One of the limitations of the study was the use of radiographic measurements alone without other measures of fracture healing, which may be inaccurate as neither hospital had digital radiography to reduce the problems. The assessment of radiological union by observing the presence of bridging callus may be unsatisfactory (Eastaugh-Waring et al., 2009). This is especially so if union does not progress adequately or if a more exact evaluation of fracture healing is required, for example, in the evaluation of treatment. <u>However, this information does not reject the aim of this study as the study did not look only at callus formation but cortices bridged, fracture gap and healing.</u>

These results used cross-tabulation and resulted in small or greatly differing sample size in the groups compared to when the participants were divided into the presence or absence of callus, fracture gap and cortices. This may have resulted in large effect sizes and, due to their non-linear nature of the legit transform, wide confidence intervals due to sparse-data bias. These results should be considered with caution, especially since some groups presented with a zero value.

Many people still lived in unstructured houses (shacks), and had no access to electricity to plug in the machine during the treatment, hence they were excluded. Patients normally live far from public transport and need to travel long distances to catch public transport and therefore they were excluded, only patients living within a 10km radius from the hospitals could be included in the study, limiting the sample size.

5.4.5 Strengths of the study

The assessor who interpreted the radiographic findings during fracture healing was a qualified radiologist.

The patients, assessors (radiologist) and the therapists were double blinded.

As the equipment was sponsored by Mediotronics, it made it easy as they delivered the machines with just the numbers; therefore, there was no suspicion as to which machine was for the control or intervention group.

All participants were compliant with the LIPUS intervention as this was ensured by continued treatment after discharge by their returning as outpatients to the hospital or the researcher treating them at home.

CHAPTER 6 CONCLUSION

6.1 MAIN FINDINGS

In answer to the research question, what is the prevalence of non-union lower limb fractures in patients in public hospitals in Johannesburg, this study gives evidence that lower limb non-union fractures in patients treated in hospitals in Johannesburg have a low prevalence when complex fractures are not considered. Results indicate that more male patients present with fracture non-union in terms of gender difference. Additionally, femur and tibia are the fracture sites that present with the highest prevalence of non-union and management of this group of patients should be considered to reduce the prevalence of non-union.

The second research question considered the factors that inform a proposed clinical pathway and outcomes of non-union fractures in the lower limb at selected public hospitals in Johannesburg. The factors, which need to be considered for a clinical pathway, include both medical and demographic factors.

The number of days these patients have lower limb non-union fractures and how the patients are expected to go in and out of hospital either for non-union that develop an infection, which leads to more days in hospital for management, was of concern. Additionally, patients with non-union fractures collect medications and/or attend rehabilitation in weekly bases hoping to fight the battle of the non-union fractures.

Several factors including the anatomical fracture site and the socio-demographic characteristics of the patients need to be considered. The current study indicated that patients with fracture non-union of the lower limbs are utilising substantial healthcare resources including hospitalisation, a number of surgeries, high medication use and receive rehabilitation therapy. Patients present with functional impairments, which affect activity participation according to the ICF. However, these health concerns may not be receiving any attention from the health team. This makes the condition cost-intensive with poor outcomes, as none of the patients had resolution of their non-union fracture over six months. Higher prevalence of comorbidities and health risk behaviours were found for the patients with that non-union lower limb fractures, especially with the presence of HIV and smoking.

When a holistic view of the participants was considered it was confirmed that non-union lower limb fracture healing also takes a toll on the emotional and physical functioning of the patient and this study found that lower limb non-union fractures could significantly reduce the quality of life of patients. Travelling to and from hospital to collect medication, to consult the doctor or rehabilitation team is a burden. Most of the patients with lower limb non-union fractures have stopped work or lost their jobs due to non-union.

A proposed clinical pathway presented for physiotherapy as an evidence-based alternative, needs to consider possible conservative management of the lower limb non-union fractures. It is clear that clinical pathways of the patients with lower limb non-union fractures is not pleasant as in the period of six-months follow-up, patients presented with detected disabilities. Therefore, the third question addressed the effects of non-invasive low-intensity pulsed ultrasound (LIPUS), which has been found to accelerate fracture healing on lower limb fracture healing. The study aimed to close the gap by studying the lower limb fractures in a population where there are numerous comorbidities, including non-union fractures, HIV, smoking and/or diabetes. The effects of LIPUS have not been reported in South Africa where patients with surgically managed lower limb fractures have a high prevalence of comorbidities. These comorbidities are of concern to the South African population because they are associated with delayed healing and non-union in patients with lower limb fractures.

In this study, low-intensity ultrasound did not seem to influence fracture healing. Callus formation, cortices bridged and fracture gap did not show any enhancement in healing between the intervention and control group at 40 days of LIPUS application on alternate days. The normal healing rate of fractures is six to 12 weeks and over an 18-week period, there was little difference in the variables indicating fracture healing and overall fracture healing between the intervention and control groups. Low-intensity pulsed ultrasound had no detrimental effect on fracture healing in the intervention group. When the participants with non-union fracture only were considered there were significant differences in callus formation, cortices bridged and fracture gap but not overall healing at 18 weeks. These findings support the use of LIPUS with patients with non-union fracture of the lower limbs, especially since this group had even higher prevalence of comorbidities than those reported for the sample in this phase of the study. These findings must be interpreted in light of the small sample size.

In terms of demographics and other comorbidities, low-intensity pulsed ultrasound efficiency did not show any significance in change of any comorbidity. The lack of impact of LIPUS in the current study could have been caused by reducing the treatment time to every second day, unlike the other published studies of every day. Unfortunately, the use of LIPUS every day in South Africa may not be possible due to limited availability of the equipment. Secondly, LIPUS in other countries is left in the patient's home and they are taught self-treatment. Leaving the equipment in a patient's home in South Africa is risky as the evidence of theft was reported, thus making the application of this technique difficult if the patient is discharged before eight weeks of treatment could be given. The median length of stay for patients with non-union fracture was found to be four months; hence, it may be possible to consider using LIPUS with these patients and reduce their hospital stay.

Logistic regression using univariate and multivariate analysis confirmed, as in other research, that gender, site of fracture and fracture management were associated with delayed callus formation and cortices bridged as was non-union fracture. This finding was not presented before was the association in a multivariate model for delayed reduction of the fracture gap and HIV.

6.2 CLINICAL IMPLICATIONS

Female patients with lower limb fractures should be monitored, considering threats of delayed healing and non-union are high. Fracture femur and tibia in the lower limb are more susceptible to lower limb delayed healing and non-union fractures.

<u>All patients involved in the clinical pathways study were on poly-medication because of constant pain and comorbidities. The relationship between the fracture healing and long term pharmaceutical use should be researched.</u>

Low-intensity pulsed ultrasound is not the ideal solution in conservative treatment management of fractures. Costs of the machine and application of the treatment is very costly both in patient and therapy time and the benefits are not shown by the therapy. Low-intensity pulsed ultrasound is not recommended in treatment of surgically managed lower limb fractures except if the patients present with non-union.

6.3 RECOMMENDATIONS

We recommend further research to develop clinical pathways to be carried out by a multidisciplinary team where the total hospital and patients’ costs are monitored.

A long-term prospective study with many participants is required to observe the implementation of clinical pathways of patients with lower limb non-union fractures.

Low-intensity pulsed ultrasound is not recommended for treatment of fractures in general in any community, as the value of the machine and time is costly to the patient and the healthcare services if the patient does not present with non-union fracture.

6.4 CONFLICT OF INTEREST

Enraf Mediotronics sponsored the both intervention and sham machine for research purposes. There is no conflict of interest between the other researchers.

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Zura R, Xiong Z, Einhorn T, et al. (2016) Epidemiology of fracture nonunion in 18 human bones. *JAMA surgery* 151: e162775-e162775.

ANNEXURES ANNEXURE 1: PHASE 1 (PART 1) DATA COLLECTION SHEET

Data collection sheet (Phase 1 – part 1)

Sheet no:

Age: **Gender:** **Dignosis:**

No	Fracture type	Gender	Age
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			
11.			
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17.			
18.			
19.			

ANNEXURE 2: ETHICAL CLEARANCE PHASE 1

R14/49 Ms Nontembiso Magida

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130952

NAME: (Principal Investigator)	Ms Nontembiso Magida
DEPARTMENT:	Physiotherapy Chris Hani Baragwanath Academic Hospital Charlotte Maxeke Johannesburg Academic Hospital & Helen Joseph Hospital
PROJECT TITLE:	Efficacy of Non-Invasive Low Intensity Pulsed Ultrasound in Healing of Non-Union Fractures in HIV Positive Patients — Phase 1
DATE CONSIDERED:	27/09/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Hellen Myezwa
APPROVED BY:	Professor A Woodiwiss, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	18/12/2013

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature ____________ Date ____________

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

ANNEXURE 3A PHASE 1 (PART 2) CLINICAL PATHWAYS QUESTIONNAIRE

Clinical Pathways questionnaire

File number: Patient No:

Diagnoses: Date of first non-union diagnoses:

Medication:

Medical Management

Traction (period): ORIF: External Fixation:

Vac Drainage: Yes/ No Other post-operative complications:

Physiotherapy: Yes/No Occupational Therapy: Yes/ No Dietician: Yes/No

Other: Yes/ No If Yes explain:

Discharge date: Mobility status at discharge: Length of stay:

Follow-up appointments (frequency):

Health related quality of life at home using ICF

Impairment:

Activity:

Participation:

Return to work: Y/N Re-admission within 6 months (frequency):

Final results of non-union fracture: Healed/ Not healed/ Amputated

ANNEXURE 3B:– SF-36

SF-36 QUESTIONNAIRE

Name:___________________ **Ref. Dr:**__________________ **Date:** _______

ID#: _______________ **Age:** _______ **Gender: M / F**

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:

In general, would you say your health is:

◯ Excellent ◯ Very Good ◯ Good ◯ Fair ◯ Poor

Compared to one year ago, how would you rate your health in general now?

◯ Much better now than one year ago
◯ Somewhat better now than one year ago
◯ About the same
◯ Somewhat worse now than one year ago
◯ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

◯ Yes, Limited a lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Lifting or carrying groceries

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Climbing several flights of stairs

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Climbing one flight of stairs

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Bending, kneeling, or stooping

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Walking more than a mile

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Walking several blocks

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Walking one block

◯ Yes, Limited a Lot ◯ Yes, Limited a Little ◯ No, Not Limited at all

Bathing or dressing yourself
◯Yes, Limited a Lot ◯Yes, Limited a Little ◯No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities
◯Yes ◯No

Accomplished less than you would like
◯Yes ◯No

Were limited in the kind of work or other activities
◯Yes ◯No

Had difficulty performing the work or other activities (for example, it took extra effort)
◯Yes ◯No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities
◯Yes ◯No

Accomplished less than you would like
◯Yes ◯No

Didn't do work or other activities as carefully as usual
◯Yes ◯No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

◯Not at all ◯Slightly ◯Moderately ◯Severe ◯Very Severe

PAIN:
How much bodily pain have you had during the past 4 weeks?

◯None ◯Very Mild ◯Mild ◯Moderate ◯Severe ◯Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

◯Not at all ◯A little bit ◯Moderately ◯Quite a bit ◯Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt downhearted and blue?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
○Definitely true ○Mostly true ○Don't know ○Mostly false ○Definitely false

I am as healthy as anybody I know
○Definitely true ○Mostly true ○Don't know ○Mostly false ○Definitely false

I expect my health to get worse
○Definitely true ○Mostly true ○Don't know ○Mostly false ○Definitely false

My health is excellent
○Definitely true ○Mostly true ○Don't know ○Mostly false ○Definitely false

ANNEXURE 4A: PHASE 1 (PART 2) AND PHASE 2 INFORMATION SHEET

Information sheet (Clinical pathways)

My name is Nontembiso Magida . I am a PhD student from University of Witwatersrand. I am conducting a study on Low intensity Pulsed Ultrasound in healing of non-union fractures. I am inviting you to take part in this study. To help you make an informed decision here are a few prepared questions and answers.

***Why am I doing this*?**

The aim of this study is to determine the clinical pathways of the patients with lower limb fractures at Chris Hani Baragwanath Academic, Charlotte Maxeke Academic, Helen Joseph, Steve Biko Academic and Kalafong Academic hospitals and to determine the effect of non-invasive low intensity ultrasound on the healing of lower limb fractures. As part of this study, I need to know how the people with fractures are managed in hospital and how those who have non-union fractures how are they managing at home if discharged before the fracture healed.

What do I expect from those participating in the study: I will request you to complete the questionnaires that will be provided so that I gather the information about your treatment and your function and how you are living after discharge.

Are there benefits to participants?: There are no benefits at this point in time but the results of the questionnaires will help to improve the service and care of the people with non-union fractures in future.

Will my information be confidential?: Care will be taken to ensure that no names are recorded. You will be given a code on the records and only researcher and research assistant that will have access to the list.

May I stop the study at any time?: If you feel you do not want to take part in the study for any reason you are free to do so. The normal treatment and services that you would need will not be affected in any way. If you should choose to participate, please sign the attached consent form and be assured you are free to stop at any time.

Thank you for your time

ANNEXURE 4B: CONSENT FORM

Ms N Magida

Informed Consent

Study title: Efficacy of non-invasive low intensity pulsed ultrasound in healing of non-union fractures in HIV positive patients.

I ……………..(name of participant) hereby accept the invitation to join the research project and give my permission on…………..(date) at………..(place) to take part in the study entitled ‘Efficacy of non-invasive low intensity pulsed ultrasound in treatment of lower limb fractures”.

I am aware that I am taking part on my will and I may stop my participation at anytime without giving any reason. I understand that my stopping participation would not prevent me from obtaining any services at the hospital and I would not be treated unfairly in anyway. Information will not be given to anyone else but that I will have access to any information related to my health status.

I am aware that the information obtained from the study will be published so that the information may be of benefit to others.

I am aware that there will be no direct payment to participate to the study except where necessary transport and telephone costs will be covered.

With the above information I understand and agree to participate in the study.

Researcher's name and signature:…………………….

Patient no: …………………………..

ANNEXURE 5: PHASE 1 (PART 2) AND PHASE 2 ETHICAL CLEARANCE – UNIVERSITY OF WITWATERSRAND

R14/49 Ms Nontembiso Magida

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150236

NAME: **(Principal Investigator)**	Ms Nontembiso Magida
DEPARTMENT:	Physiotherapy Chris Hani Baragwanath Academic Hospital Charlotte Maxeke Johannesburg Academic Hospital Helen Joseph Hospital Steve Biko Academic and Kalafong Hospitals
PROJECT TITLE:	Efficacy of Non-Invasive Low Intensity Pulsed Ultrasound in Healing of Non-Union Fractures
DATE CONSIDERED:	27/02/2015
DECISION: **CONDITIONS:**	Approved unconditionally Aditional study sites 20/12/2016
SUPERVISOR:	Prof Hellen Myezwa
APPROVED BY:	Professor C Feldman, Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	15/04/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Administrators in Room 301, 302,304,Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193,University of the Witwatersrand.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in February and will therefore be due in the month February each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature   Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

ANNEXURE 6: PHASE 1 (PART 2) AND PHASE 2 ETHICAL CLEARANCE:

UNIVERSITY OF PRETORIA

The Research Ethics Committee, Faculty Health Sciences, University of Pretoria complies with ICH-GCP guidelines and has US Federal wide Assurance.

- FWA 00002567, Approved dd 22 May 2002 and Expires 03/20/2022.
- IRB 0000 2235 IORG0001762 Approved dd 22/04/2014 and Expires 03/14/2020.

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

Faculty of Health Sciences Research Ethics Committee

31/08/2017

Approval Certificate
New Application

Ethics Reference No: 349/2017

Title: Efficacy of non-invasive low intensity pulsed Ultrasound in healing of lower limb fractures in South Africa

Dear Miss Nontembiso Magida

The **New Application** as supported by documents specified in your cover letter dated 10/07/2017 for your research received on the 10/07/2017, was approved by the Faculty of Health Sciences Research Ethics Committee on its quorate meeting of 30/08/2017.

Please note the following about your ethics approval:

- Ethics Approval is valid for 1 year
- Please remember to use your protocol number (**349/2017**) on any documents or correspondence with the Research Ethics Committee regarding your research.
- Please note that the Research Ethics Committee may ask further questions, seek additional information, require further modification, or monitor the conduct of your research.

Ethics approval is subject to the following:

- The ethics approval is conditional on the receipt of **6 monthly written Progress Reports**, and
- The ethics approval is conditional on the research being conducted as stipulated by the details of all documents submitted to the Committee. In the event that a further need arises to change who the investigators are, the methods or any other aspect, such changes must be submitted as an Amendment for approval by the Committee.

We wish you the best with your research.

Yours sincerely

*** Kindly collect your original signed approval certificate from our offices, Faculty of Health Sciences, Research Ethics Committee, Tswelopele Building, Level 4-60*

Dr R Sommers; MBChB; MMed (Int); MPharMed,PhD
Deputy Chairperson of the Faculty of Health Sciences Research Ethics Committee, University of Pretoria

The Faculty of Health Sciences Research Ethics Committee complies with the SA National Act 61 of 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 and 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes, Second Edition 2015 (Department of Health).

☎ 012 356 3084 fhsethics@up.ac.za http://www.up.ac.za/healthethics
✉ Private Bag X323, Arcadia, 0007 - Tswelopele Building, Level 4, Room 60, Gezina, Pretoria

ANNEXURE 7: LETTER FROM KALAFONG ACADEMIC HOSPITAL

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

KALAFONG HOSPITAL
PRIVATE BAG X396
PRETORIA
0001

ENQUIRIES : MS NT LEDIGA
TEL : 012 318 6995
FAX : 012 373 6791
EMAIL : Neily.Lediga@gauteng.gov.za
REF : KPTH 55/2016

TO: MS NONTEMBISO MAGIDA

RE: CONDITIONAL PERMISSION TO CONDUCT RESEARCH

TITLE: EFFICACY OF NON-INVASIVE LOW INTENSITY PULSED ULTRASOUND IN HEALING OF LOWER LIMB FRACTURES IN SOUTH AFRICA

Conditional permission is hereby granted for the research to be conducted at **Kalafong Provincial Tertiary Hospital**. Please note that full approval will be granted on receipt of Ethics approval.

Kind regards

DR K.E LETEBELE-HARTELL
SENIOR MANAGER: MEDICAL SERVICES

DATE: 2016/12/05.

Ethics approval submitted: YES NO

Approved.

DR K.E LETEBELE-HARTELL
SENIOR MANAGER: MEDICAL SERVICES

DATE:

ANNEXURE 8: LETTER FROM STEVE BIKO ACADEMIC HOSPITAL

Student Ethics Committee: 10 copies

APPLICATION TO CONDUCT A CLINICAL TRIAL/EVALUATION

Faculty of Health Sciences Research Ethics Committee
University of Pretoria
Pretoria Academic Hospital
Tel: (012) 339 8612
Fax: (012) 339 8587
E Mail: manda@med.up.ac.za - Main Committee
E Mail: dbehari@med.up.ac.za - Student Committee

Soutpansberg Road - MRC-Building - Level 2 - Room 19
Private Bag x 385 – Pretoria – 0001

GAUTENG HEAD OFFICE USE	
FILE REFERENCE	
PROTOCOL NUMBER	
REPORT DUE DATE	

GENERAL INFORMATION AND AGREEMENT BY APPLICANT

1. APPLICANT:
Investigator Nontembiso Magida

1.1 FIRM:
Name of firm : Physiotherapy
Telephone Number: 012 356 3230 Fax Number: 086 658 9293
E.Mail address: nontembiso.magida@up.ac.za
N/A
Postal Address: BOX 15225 Farrarmere 1518
Name of representative:
Nontembiso Magida
Designation: Physiotherapy Lecturer

1.1.2 HOSPITAL MEDICAL APPOINTEE:
Investigator Name Nontembiso Magida
Designation/Rank: Physiotherapy Lecturer
Telephone Number: 012 356 3230 / 082 963 8547
Fax Number: 086 658 9293
Email address: nontembiso.magida@up.ac.za
Name of Hospital: Steve Biko Academic Hospital
Postal Address of Hospital: 0001

1.1.3. FULL TITLE OF CLINICAL TRIAL: EFFICACY OF Non-invasive low intensity pulsed ultrasound in healing of lower limb fractures in South Africa

1.1.4. OUTLINE DETAILS OF PREVIOUS TRIALS/EVALUATIONS CONDUCTED IF ANY:
NONE

1.2 TRIAL/EVALUATION PRODUCT (S) Name the product(s) and state the mode of application(s)
1.2.1 NONE
1.2.2 NONE.

1

1.3 REGISTRATION N/A

1.3.1 PHARMACEUTICAL

1.3.1.1 State MEDICINE CONTROL COUNCIL registration number:

1.3.1.2 If not registered state MCC trial approval number and attach official approval letter.

1.3.2 NON-PHARMACEUTICAL

1.3.2.1. State registration/code number U04868316

1.3.2.2 What is the estimated cost of these investigations? NO costs

1.3.2.3. Who will be responsible for these costs? The Researcher (N Magida)

1.3.2.4. What other equipment will be required for the trial? Low intensity pulsed ultrasound (researcher to provide)

1.3.2.5 What arrangements have been made for those investigations and with whom?
Mediotronics sponsored the equipment

1.4 ARE ANY SPECIAL PRECAUTIONARY MEASURES TO BE TAKEN AND BY WHOM?
NO precautions specifically, the researcher will monitor if any arise.

1.5 INDICATE EXPECTED DATE OF TRIAL / EVALUATION REPORT :

DAY	MONTH	YEAR
01	November	2016

1.6 INDICATE NUMBER OF PATIENTS INVOLVED :

		9	0

1.7 THE NAME OF THE HEAD OF THE DEPARTMENT:
Prof Joyce Mothabeng

1.8 WILL SUFFICIENT TRIAL/EVALUATION MATERIAL BE SUPPLIED? Yes ✓ No

1.9. INVESTIGATIONS

1.9.1 WHAT LABORATORY AND OTHER INVESTIGATIONS WILL BE REQUIRED OVER AND ABOVE THOSE NORMALLY REQUIRED. X-rays as per hospital routine

1.10. AGREEMENT BY APPLICANT

1.10.1. The applicant(s) agree(s) as follows
1.10.2. To conduct the trial/evaluation recorded in and under the conditions set out in this application form.
1.10.3. To conduct this trial/evaluation at no additional expense to theGauteng Department of Health whatsoever.

1.10.4. To accept full responsibility for any or all-possible harmful effects on a patient using my/our/ the product recorded in his application form.

1.10.5. To exonerate the Gauteng Department of Health from all liability of damages, legal,financial or otherwise, including my claim instituted by a patient using my/ our/ the product recorded in this application form, but excluding negligence on the part of the medical officer and/ or employee of the Gauteng Department of Health using the said product on the patient's concerned. Provided that the medical officer and/ or employee is not the applicant.

1.10.6. To inform the Superintendent General: Gauteng Department of Health and other relevant authorities should it be deemed necessary to deviate from protocol or stop this trial/ evaluation.

1.10.7. To make available without delay all the results of this trial/ evaluation to the Superintendent General: Gauteng Department of Health.

1.10.8. I/ We understand that the Superintendent-General: Gauteng Department of Health having allowed this trial/ evaluation to be conducted places himself or herself or the Gauteng Department of Health under no obligation whatsoever and to leave the final choice of the institution where the trial/ evaluation will be conducted to the Superintendent- General: Gauteng Department of Health.

THE APPLICANT MUST SIGN HERE

APPLICANT- INVESTIGATOR			DATE		
Signature	Initial(s)	Surname	Day	Month	Year
[signature]	N	Magida	19	10	2016

Designation/ Rank: Physiotherapy Lecturer

FIRM - IF THERE IS A FIRM INVOLVED- THEY MUST SIGN HERE

MANAGING DIRECTOR OR REPRESENTATIVE			DATE		
Signature	Initial(s)	Surname	Day	Month	Year

Designation/ Rank: ____________________

IT IS VERY IMPORTANT THAT 2 WITNESSES MUST SIGN IF A FIRM IS INVOLVED!

WITNESSES			DATE		
Signature	Initial(s)	Surname	Day	Month	Year
1.					
2.					

2. INITIAL CONSENT BY DEPARTMENTAL HEAD

2.1 I E. van Niekerk head of Physiotherapy department of Steve Biko Academic hospital in consultation with the Chief Executive Officer / Superintendent of this Hospital grant permission to submit an application to conduct a clinical trial/evaluation to the Chairperson (s) of the relevant Ethics, Research and Therapeutic Committees of this Hospital.

2.2 The officer conducting the trial/evaluation will be Nantembiso Magida.

Designation / Rank Physiotherapy Lecturer

3

THE HEAD OF THE DEPARTMENT MUST SIGN HERE!

HEAD OF DEPARTMENT			DATE		
Signature	Initial(s)	Surname	Day	Month	Year
	E.	Van Niekerk.	7	11	2016.

THE APPLICANT MUST SIGN HERE

TRIALIST-INVESTIGATOR			DATE		
Signature	Initial(s)	Surname	Day	Month	Year
	N	Magida	21	10	2016

THE APPLICANT WHO APPLIES FOR THIS STUDY MUST SEE TO IT THAT THE SUPERINTENDENT / C.E.O. OF THE HOSPITAL WHERE THE STUDY WILL BE DONE, SIGN HERE BEFORE THE ETHICAL COMMITTEE RECEIVE THIS APPLICATION FORM.

2.3. APPROVAL BY HOSPITAL SUPERINTENDENT:

I DR M.E. KEMOSI CHIEF EXECUTIVE OFFICER STEVE BIKO ACADEMIC HOSPITAL Chief Executive Officer / Superintendent of ______ Hospital hereby agree that this trial / evaluation be conducted in the ____________ Department of this hospital.

The officer conducting the trial will be : ____________

The officer controlling supplies will be: ____________

HOSPITAL C.E.O. / SUPERINTENDENT			DATE		
Signature	Initial(s)	Surname	Day	Month	Year
	M.E.	KEMOSI	17	11	2016

3. APPROVAL BY SUPERINTENDENT GENERAL : GAUTENG DEPARTMENT OF HEALTH – TRIAL / EVALUATION

SUPERINTENDENT GENERAL			DATE		
Signature	Initial(s)	Surname	Day	Month	Year

ANNEXURE 9: PHASE 2 DATA COLLECTION SHEET

PHASE 2 DATA COLLECTION SHEET

RESEARCHER: NONTEMBISO ASSISTANCE: MACHINE NUMBER:

PATIENT No: AGE: GENDER: FILE #:

DIAGNOSES: DATE OF ASSX:

HOME ADDRESS: CELL NO:

NEXT OF KIN: CELL NO:

Comorbidities (please specify year of diagnoses/year started):

- ☐ HIV/AIDS
- ☐ DIABETIC
- ☐ CANCER
- ☐ SMOKING
- ☐ HYPERTENSION

X-RAYS RESULTS ON ADMISSION:

X-RAY RESULTS AT 6 WEEKS:

X-RAY RESULTS AT 12 WEEKS:

PRESENT MEDICAL HISTORY	PAST MEDICAL HISTORY
FRACTURE MANAGEMENT ☐ ORIF ☐ EXTERNAL FIXATION ☐ OTHER	COMPLICATIONS
CURRENT MEDICATIONS	OTHER
DAY 1 Rx:	DAY 2 Rx:
DAY 3 Rx:	DAY 4 Rx:
DAY 5 Rx:	DAY 6 Rx:
DAY 7 Rx:	DAY 8 Rx:

DAY 9 Rx:	DAY 10 Rx:

DAY 11 Rx:	DAY 12 Rx:
DAY 13 Rx:	DAY 14 Rx:
DAY 15 Rx:	DAY 16 Rx:
DAY 17 Rx:	DAY 18 Rx:
DAY 19 Rx:	DAY 20 Rx:

ANYTHING TO BE NOTED

ANNEXURE 10 INTENTION TO TREAT ANALYSIS

An intention to treat (ITT) analysis was also completed on the data as literature indicates this analysis is essential in avoiding bias in the analysis of randomised trials (Newell, 1992). Although controversy exists about whether ITT analysis should be completed with the strict view being that no analysis with missing outcome can be described, the European Medicines Agency suggested that missing data should be estimated in clinical trials (European Medicines Agency, 2010). It has been suggested that an ITT analysis should be completed to accommodate the loss of outcomes and missing data as emphasised by Consolidated Standards of Reporting Trials (CONSORT) guidelines to provide an unbiased estimate of treatment effect (Gupta, 2011). Since the loss of outcome X-rays in this study was greater than 20%, the results of the ITT analyses were presented separately from the per protocol analysis.

The missing data in this study could be considered as missing at random (MAR), based on the loss of X-rays or not being taken due to the healthcare system in which the patients were treated. An analysis suited to MAR, a Generalised Estimation Equation (Westgeest et al. 2016) analysis to analyse (ITT) was used. The GEE analysis is suited to MAR for longitudinal data with small sample sizes (Shen and Chen, 2012; Wang, 2014).

Comparison of fracture healing in intervention and control groups over time

Callus formation

At six, 12 and 18 weeks, the ITT analysis results confirmed a greater increase in callus formation for the intervention group at all three periods. Although there was no significant difference between the intervention and control groups in callus formation at six and 12 weeks, when the missing data was analysed the difference between the groups at 18 weeks was significant.

Cortices bridged

The ITT results at six and 12 weeks indicated a higher percentage of participants in the intervention group had no cortices and there was no significant difference between the two groups. At 18 weeks a significantly higher percentage (84.44%) of participants in the intervention group had cortices present compared to those (53.06%) in the intervention group with a significant difference (p=0.013).

Fracture gap

The ITT analysis indicated similar results to the per protocol results with a higher percentage of patients in the control group (40; 83.63%) having a fracture gap at six and 28 (57.14%) at 12 weeks. The fracture gap was present in a lower percentage of participants (23; 51.11%) in the intervention than the control group (31; 63.27%) group at 18 weeks, although this was not significant.

Overall healing

The ITT analysis showed similar results with no healing at six weeks and a small percentage of healing in both the intervention and control group at 12 and 18 weeks. There was no significant difference between the groups for overall healing at any of the assessment periods. Although few patients had fractures healed at 12 weeks, the percentage was higher in the intervention group on the ITT analysis.

Summary

The ITT analysis indicates that the intervention group had a higher percentage of participants with callus formation and overall healing at six, 12 and 18 weeks. The control group had more cortices bridged and no fracture gap at six and 12 weeks, but the intervention group has a significantly higher percentage of participants with cortices bridged and a lower percentage with fracture gap at 18 weeks. Although by 18 weeks the percentage of participants in the intervention group with positive signs of fracture healing was higher, this difference was not significantly greater than for the control group, and the difference in radiological outcomes differed over the three periods. It would appear, as with the callus formation, the LIPUS intervention may have accelerated callus formation in the first six weeks with a significantly greater percentage of participants having cortices bridged at 18 weeks on ITT analysis.

Change in within group outcomes related to fracture healing over time.

Callus formation

The results for the ITT analysis for callus formation within the intervention and control group differed from the per protocol analysis in that both groups at six to 12 weeks had significant change to callus formation from no callus formation. The control group had one participant who changed from having callus to no callus formed with an odds ratio of 0.07 (CI 0 - 0.46).

At 12 – 18 weeks, as in the per protocol analysis, neither group showed significance in the change for the presence of callus, but in the control group nine participants with an odds ratio of 1.28 (CI=0.42 - 4.06) moved from callus formation to no callus formation. For the intervention group at 12-weeks, the odds for change in the presence of callus was 0.25 (CI=0-2.52) times lower than no change or an absence of callus formation. This indicates higher odds ratio change for no callus formation in the control group over this period was higher.

When the entire period from six to 18 weeks was considered, both groups showed for the per protocol analysis statistical significance in terms of change in the presence of callus formation. However, the ITT analysis indicated the control group had greater likelihood of change from callus to no callus formation in nine participants over the six-18 weeks as the odds were 0.42 (CI= 0.15-1.00) times lower for callus formation in this group.

This is confirmed in Figure 5.3, where over the entire period of six-18 weeks the ITT analysis indicated the intervention group had higher mean callus formation throughout the study when missing data was accommodated for 18 weeks.

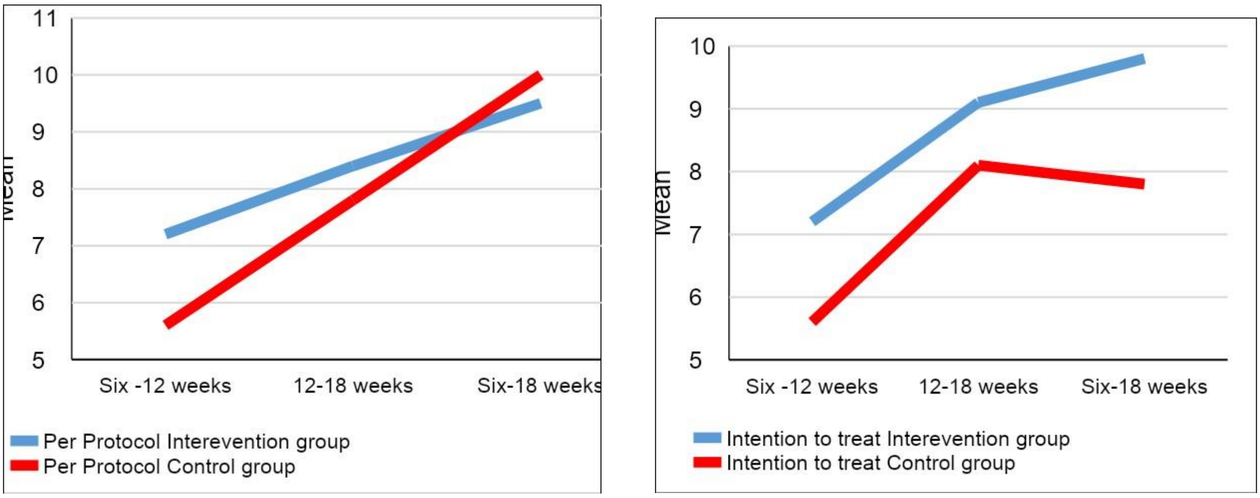


Figure A1 Callus formation over time – per protocol and intention to treat analysis

Cortical bridging

The results of cortical bridging on the ITT analysis reflected those on the per protocol analysis for the study period. The difference for cortical bridging was also significant on the ITT analysis at six-12 weeks and six-18 weeks (Figure 5.4).

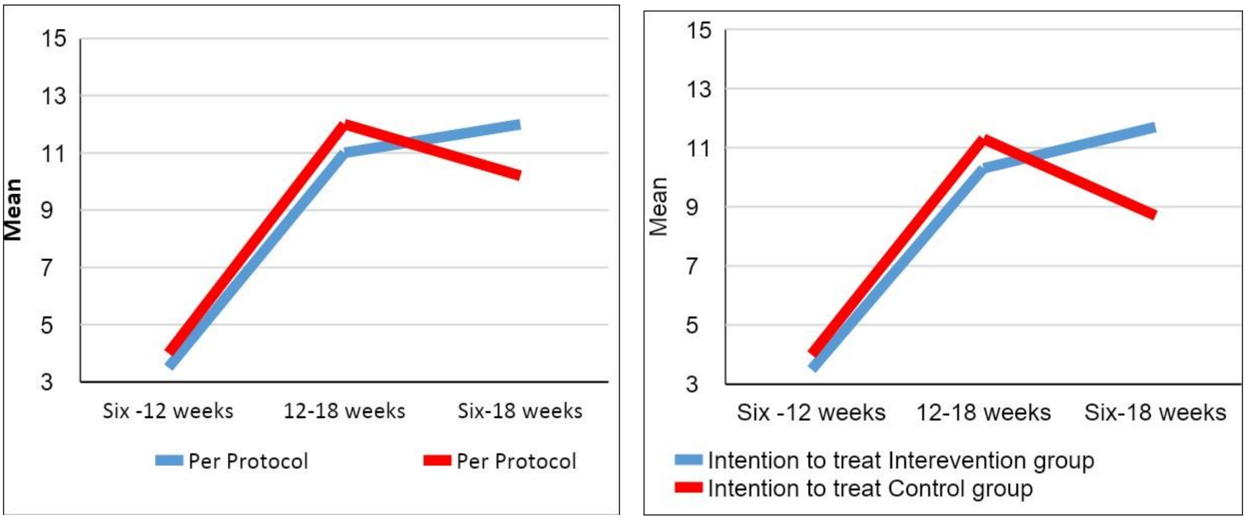


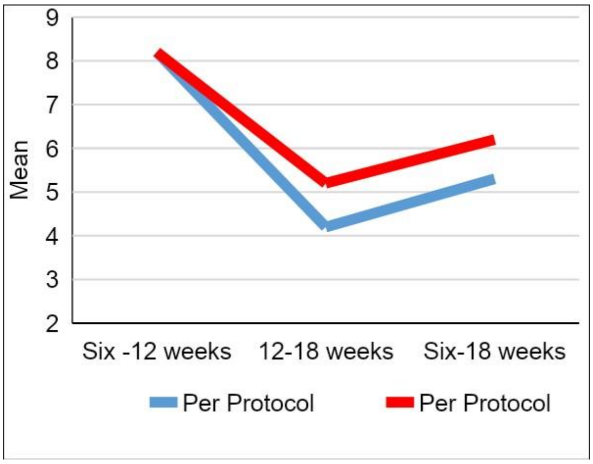
Figure A2 Cortices bridged over time – per protocol and intention to treat analysis

At 12-18 weeks, the odds ratio for change from cortices bridged to no cortices bridged in control group was higher at 16 (CI=2.48-670.96), which was statistically significant (p<0.003), while in the intervention group odds ratio in this period was only 0.2 (CI=0-1.78).

On the ITT analysis from six to 18 weeks however, the control group had an odds ratio of 0.26 (CI=0.07 - 0.72) change from cortices bridged to no cortices bridged in the control group compared to odds of zero (CI=0 - 0.14) for the intervention group. Over the entire study period of six-18 weeks, the intervention mean cortices bridged was greater for the intervention group.

Fracture gap

The results for the ITT analysis were similar to those for the per protocol analysis and had statistical significance for the intervention and the control group (p=0.000) for the reduction of the fracture gap at six -12 weeks. The intervention group however had odds of 25 (CI=4.09 - 1026.40) for less change in the presence of the fracture gap, while the control group had an odds ratio of zero (CI =4.66 – 0) for less change in the presence of the fracture gap.



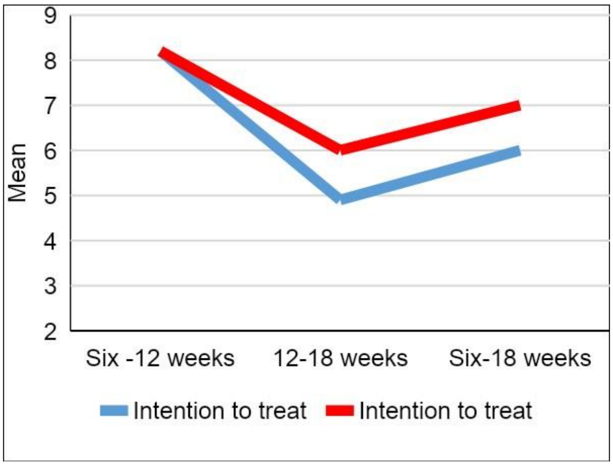


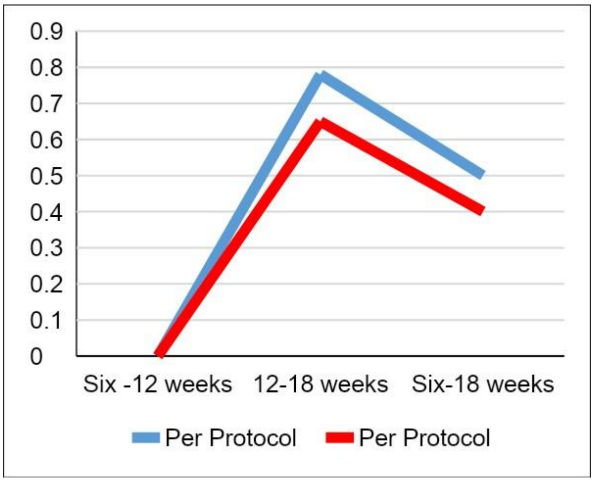
Figure A3 Presence of fracture gap over time – pre protocol and intention to treat analysis

On the ITT analysis, both groups showed statistically significance for change in the fracture gap with the intervention group having odds for change in the fracture gap 0.16 (CI= 0.01 - 0.74) and the control group of 0.23 (CI=0.042 - 0.83) between 12-18 weeks, where the ITT analysis indicated 12 and 13 participants changed from no fracture gap to a fracture gap.

As confirmed in Figure 5.6, the fracture gap resolution was lower in both groups between 12-18 weeks. The ITT analysis was also statistically significant at six -18 weeks and that mean fracture gap reduction was greater in the intervention group. The odds ratio for change from no fracture gap to fracture gap was 0.56 (CI=1.63-30.18) for the intervention group and 0.55 (CI=1.20-51.06) for the control group for weeks six-18, which differed from the per protocol analysis. These results were statistically significant indicating similar results for both groups.

Overall healing

The results on the ITT analysis for overall healing were similar to those for the per protocol analysis with greater healing in both groups at 12-18 weeks. As for the per protocol analysis, only participants in the control group had changed from overall healing to no overall healing with a slightly higher odds ratio of two (0.10 - 117.99).



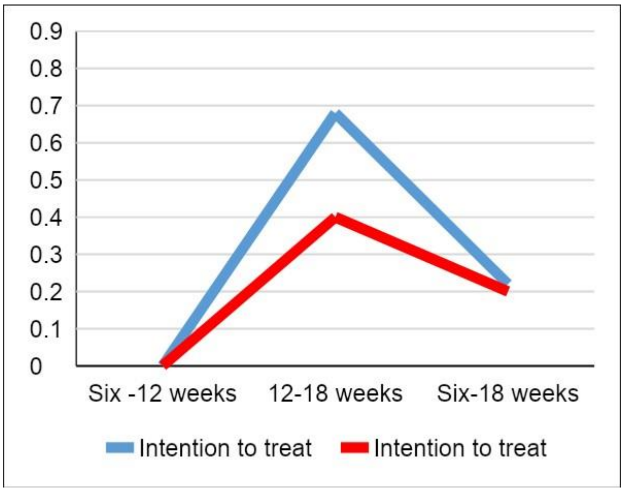


Figure A4. Overall healing over time – per protocol and intention to treat analysis

This finding was confirmed in Figure 6.6, where the intervention group had greater overall healing on the ITT analysis at 12-18 weeks.

Summary

The ITT analysis for the change within the groups indicates the intervention group and control groups had similar odds for fracture healing between six to 12 weeks except for callus formation, which was greater by six weeks and during the six-12 periods for the intervention group. The odds ratio for change from callus formation or cortices bridged, no fracture gap and overall healing to no callus formation or cortices bridged, a fracture and no overall healing was higher in the control group, indicating more consistent healing in the intervention group between 12-18 weeks with lower odds ratios. This confirmed the findings presented in the per protocol analysis that the LIPUS intervention may have protected the intervention group from as much deterioration in fracture healing as seen in the control group.

The ITT analysis over the entire period, from six to 18 weeks, indicated the intervention group achieved greater mean callus abortion, cortical bridging and reduction of the fracture gap than the control group

Influence of demographic, medical and health status variables on fracture healing.

Intention to treat analysis was used to determine the relationship between the outcomes related to fracture healing at six, 12, and 18 weeks and demographic, medical and health status variables. The multivariable analysis adjusted for time period/intervention and control group interaction and univariate analysis for the single variables in the model were used.

Callus formation

When compared to the per protocol analysis, the ITT analysis differed in that the control group also showed a significant result (p=0.002) for the 18 week period. All other variables that significantly influenced callus formation were similar to the per protocol analysis for gender, fracture site, fracture management and non-union fractures. The differences in the multivariate regression were for HIV status, where patients had an odds ratio of 2.85 (CI=1.23-5.73) for significantly decreased callus formation (p=0.013) in lower limb fractures on the ITT analysis. Hypertension in patients with lower limb fractures also significantly (p=0.019) affected callus formation on the ITT analysis, with odds ratio of 4.21 (CI=1.24-14.00).

Cortical bridging

As for the per protocol analysis, cortical bridging was significantly influenced by time, gender and fracture management. Differences were found for the ITT analysis in that nonunion fracture significantly influenced the bridging of cortices with an odds ratio on univariate analysis of 0.30 (CI=0.14-0.63.) (p=0.001) and 0.25 (0.09-0.72) (p=0.010) in the multivariate analysis. As for callus formation, cortical bridging in the ITT analysis was influenced by HIV status where patients had an odds ratio of 2.73 (CI=1.39-5.400) for significantly decreased cortical bridging (p=0.003) in lower limb fractures and hypertension, which also significantly (p=0.046) affected cortical bridging with odds ratio of 2.96 (CI=1.02-8.62).

Fracture gap

The time influence on fracture gap was similar to the per protocol analysis. The ITT analysis indicated significant influence of gender and age, with the analysis on gender showing a significant association to the presence of a fracture gap for with odds of 2.26 (CI=1.29-3.97) on univariate analysis, and 2.26 (CI=1.13 – 4.54) on multivariable analysis in female participants. The presence of a fracture gap was also significantly influenced by age with odds of 0.97 (CI=0.95-0.99) on univariate analysis and 0.95 (CI=0.92 – 0.97) on multivariable analysis with older participants having retention of a fracture gap.

On multivariate analysis, the fracture site and fracture management on reduction of the fracture gap showed a significant relationship (p=0.018) for a tibia/fibula fracture and a fracture gap with odds ratios 0.35 (CI=0.15-0.83), as well as between fracture management and fracture gap (p=0.002) of lower limb fractures with odds ratio of 3.89 (1.62-9.35) when ORIF is used.

For health factors on the ITT analysis, a significant relationship (p=0.078) between the presence of a fracture gap where non-union was diagnosed was found in the multivariate analysis with an odds ratio of 0.41 (CI = 0.16 -1.10) on the multivariate ITT analysis. On both univariate and analysis with odds ratio of 2.23 (CI=1.30-2.80) and multivariate analysis with odds ratio of 3.16 (CI =1.64 -6.09) was smoking. Similar results were found in the ITT analysis for univariate analysis with odds of 0.54 (CI=0.32-0.91) and multivariate analysis with odds of 0.26 (CI= 0.13-0.51) for HIV status. Diabetic participants also had odds ratio of 3.42 (CI=1.23-9.46) for decreased presence of a fracture gap in lower limb fractures on the multivariate analysis with odds ratio of 3.42 (1.23-9.46).

Overall healing

The interaction of lower limb fracture healing and time was calculated for the control and intervention groups using univariate and multivariate analysis on ITT. The results show there was no significant interaction between healing and time or any other variables.

Summary

When all factors affecting fracture healing were considered using the ITT analysis:

- The intervention and control groups were more likely to have callus, cortices bridged and absence of a fracture gap at 12 and 18 weeks.
- Female patients were less likely to have callus formation and cortices bridged than males, and present with fracture gaps when gender is considered as a single factor and in combination with all factors.
- Age was more likely to influence the presence of a fracture gap when gender was considered as a single factor and in combination with all factors.
- Participants with a tibia/fibula fracture were likely to have a less callus formation considered as a single factor and a fracture gap in combination with all factors.
- All participants with ORIF were likely to have less callus formation and fewer cortices bridged when considered as a single factor and the presence of a fracture gap when considered in combination with other factors.

- All participants diagnosed with non-union were likely to have less callus formation and fewer cortices bridged when considered as a single factor, and the presence of a fracture gap when considered in combination with other factors.
- All HIV positive participants were likely to have less callus formation and fewer cortices bridged when considered in combination with other factors, and a greater presence of a fracture gap considered as a single factor and in combination with other factors.
- All participants who were smokers were likely to have greater presence of a fracture gap when considered as a single factor and in combination with other factors
- All participants who were hypertensive were likely to have less callus formation and cortices bridged in combination with other factors
- All participants who were diabetic were more likely to have a greater presence of a fracture gap in combination with other factors

The ITT analysis indicated a higher number of factors influencing callus formation, cortices bridged and fracture gap resolution in the participants with health factors and comorbidities in particular affecting fracture healing.

ANNEXURE 11 TURNITIN REPORT

Magida final thesis

ORIGINALITY REPORT

%13	%9	%9	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.spinedragon.com Internet Source	%1
2	www.ncbi.nlm.nih.gov Internet Source	%1
3	link.springer.com Internet Source	%1
4	"European Surgical Orthopaedics and Traumatology", Springer Science and Business Media LLC, 2014 Publication	< %1
5	worldwidescience.org Internet Source	< %1
6	wiredspace.wits.ac.za Internet Source	< %1
7	lrd.yahooapis.com Internet Source	< %1
8	www.scribd.com Internet Source	< %1