Treating Achilles tendon pain and function – A feasibility study of High-Volume Ultrasound Guided Injections Verses Eccentric Loading Exercises

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ABSTRACT

Introduction

Non-insertional Achilles tendinopathy is a common overuse injury which affects the midportion of the Achilles tendon. It is frequently seen in patients between the age of 30-50 years who participate in sport or other physically demanding leisure or work activity. It is characterised by pain, impaired function and swelling around the affected tendon. The most common non-operative treatment is an eccentric loading exercise programme which has been shown to give variable short and long-term results. However, it is long (12 weeks), laborious (twice a day 7 days per week) and sometimes painful to perform. As an alternative some authors have shown a reduction in pain and improved function by injecting a high volume of saline around the effected tendon using ultrasound guidance. Unfortunately, the quality of these studies is poor, with no Randomised Control Trials to date. Therefore, the aim of this study was to examine the feasibility of conducting a future RCT, comparing high volume ultrasound guided injections of saline solution (HVUGI) with eccentric loading exercises for the treatment of non-insertional Achilles tendinopathy.

Method

Thirty-three patients took part in a two-arm randomised feasibility study. They were individually randomised via an online computer randomiser to either a treatment group who received a HVUGI or a control group who carried out a 12-week eccentric loading exercise programme. Primary outcomes included eligibility rate, recruitment rate, retention rate and adverse events. Secondary outcomes included measuring the effect on pain and function of HVUGI compared with eccentric loading exercises using the VISA-A (Victoria Institute of Sport Assessment Achilles) patient reported outcome measure. In addition, the effect of the treatment and control interventions on tendon thickness and neovascularity were measured. In the control group, adherence to the exercise regime was measured through a self-reported diary.

Results

During a six-month period 63 patients were referred to the department of orthopaedics in a large Scottish Teaching Hospital with Achilles tendon pain. Of those, 43 (68%) were considered eligible and 33 (77%) agreed to take part in the study. Of the 33 randomised (treatment group =14, control group 19) two were excluded (1 from each group) because of abnormal ultrasound scans. Eight subjects were lost to follow-up at 12 weeks resulting in a retention rate of 74% (n=23). Adherence to the eccentric loading programme was 74% when recording the number of exercise sessions completed as a percentage of the total suggested. Although improved function and reduced pain were observed in both groups, reflected by an increase in the mean VISA-A score, no significant difference was noted between the groups. No differences were observed in the secondary physiological measurements of tendon thickness and neovascularity either. However, caution regarding the outcome measures should be exercised due to the purposely small sample size.

Conclusion

This study identified some key issues which could challenge the feasibility of carrying out a future RCT. This included issues around recruitment, retention and adherence to the eccentric loading exercise programme. It was also observed that this study failed to assess any early improvements in function and reduction in pain when comparing the control and treatment groups. Additionally no economic evaluation was carried out as part of this study and should be a future consideration. Therefore, it is suggested that a pilot study is carried out with modifications made to improve areas of deficit and implement changes which include earlier evaluation of pain and function and an economic evaluation. Only if the areas of deficit show improvement to an agreed threshold should a future RCT be considered.

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CHAPTER 1 INTRODUCTION TO THE STUDY

1.0 Background

Non-insertional Achilles tendinopathy is a common overuse injury most often seen in patients between the ages of 30-50 years who actively participate in sport or other physically demanding leisure or work activities (Kingma et al., 2001). Although mostly predominant in the physically active it is reported that about 33% of all cases occur in more sedentary people (Luscombe et al., 2003). It has been described as a clinical triad of pain, impaired function and swelling in and around the Achilles tendon (Longo et al., 2009). This clinical triad is often accompanied with loss of normal collagenous architecture and neural and vascular ingrowths (neovascularity). Neovascularity is thought to be linked to the accumulation of the neurotransmitter Substance P commonly found in symptomatic tendons (Wilde et al 2011) whilst the swelling is associated with replacement of the disordered collagenous architecture with amorphous mucinous material (Pearce and Tan 2016).

Pain is the cardinal symptom which is principally intermittent and associated with loading of the tendon during activity but, which may progress to constant pain if left untreated. Therefore, the primary focus of any treatment intervention should be a reduction in pain to help facilitate improved function and early mobilisation. Alongside this focus on pain reduction some intervention studies have also evaluated changes to the tendon thickness and neovascularity seen in non-insertional Achilles tendinopathy. Several authors have demonstrated that a reduction in pain and improved function is accompanied by a reduction in neovascularity and swelling (Ohberg et al., 2004, Ohberg and Alfredson 2005, Yang et al., 2012). However, these are contrary to the findings of a more recent systematic review, which failed to find a similar positive correlation between a reduction in neovascularity and pain (Drew et al., 2014). Although it is right and proper to focus on a reduction in pain it is imperative that the effect of treatment on these physiological changes are studied to help inform our understanding and shape future research in tendon pathology and management.

Epidemiological data reporting on the incidence of non-insertional Achilles tendinopathy has tended to report separately on the incidence rates in athletes and those within the general population. In surveys of athletes an annual incidence rate of about 9%, was reported by Clements et al., (1984), whilst the incidence of Achilles tendon injury in runners one month prior to the 2007 Rotterdam Marathon was found to be around 7.4% (Van Middelkoop et al., 2008). In comparison a survey of GP practices in the Netherlands estimated the incidence of

non-insertional Achilles tendinopathy to be 2.35 per 1000 registered patients with a reported average age of 43.3 years (De Jonge et al., 2011). Although as expected the reported incidence was lower than that reported in athletic populations, the authors did suggest that this may well be an underestimate because of changes in legislation in 2006 allowing individuals to self- refer to a physiotherapist or sports physician without first visiting their GP. Therefore, a concurrent survey of physiotherapy and sports medicine practices may have provided a more accurate estimate of the incidence within the Dutch population surveyed. Sayana and Maffulli (2007) reported a considerable proportion of patients presenting to their clinic with Achilles tendon pain was "non-athletic" although they failed to provide any quantitative data to support their reported observations.

A wide variety of treatment approaches, both non-surgical and surgical, have been described in the literature. Non-surgical approaches include alteration to training or activity patterns, addressing lower limb malalignment, eccentric loading exercises (exercises whereby the tendon is lengthened under tension), use of Non-Steroidal Anti-inflammatory Drugs (NSAID) and injection therapy. Studies have reported injecting the tendon with hydrocortisone, plasma rich protein, vascular sclerosing agents as well as high volume injections of saline sometimes with the addition of small amounts of other drugs such as local anaesthetic, hydrocortisone and Aprotinin (Willberg et al., 2008, Coombes 2010, van Sterkenburg et al., 2010, Murawski et al., 2014). However, a systematic review carried out by Kearney et al., (2015) reported that there was insufficient evidence from Randomised Control Trials (RCTs) to draw conclusions or support the routine use of injection therapies in the treatment of Achilles tendinopathy. Maffulli et al., (2004) reported the increased risk of rupture, subcutaneous atrophy and skin depigmentation associated with the use of corticosteroid injections coupled with the inconclusive evidence regarding their effectiveness in reducing pain and improving function, provided no good scientific reason to support their continued use. It is this increased risk of rupture that has prompted orthopaedic and radiology departments in Scotland to stop administering corticosteroid injections for Achilles tendinopathy or tendons in general although the Principal Investigator is aware of their limited use in patients with known rheumatological disorders.

Currently the mainstay of non-surgical management is eccentric loading exercises which have been shown in the literature to provide variable short- and long-term results. Mafi et al. (2001) reported 82% of athletic patients in their study were able to return to pre-injury levels of activity following an eccentric loading exercise programme whilst only 54% of non-athletic subjects in

a study by Sayana and Maffulli (2007) improved (did not require any further treatment) following the same exercise programme. Although results are variable and suggest a reduced effectiveness in the general population the continued use of eccentric loading exercises provides an economical option requiring minimal clinical intervention and therefore an attractive option in an NHS with finite resources.

The mechanisms by which eccentric loading exercises work are poorly understood. The most popular concept is that structural adaptations referred to as hypertrophic changes occur in the tendon due to greater load created in the tendon resulting from the eccentric exercises (Stanish and Curwin 1986, Alfredson et al 1998). However, Rees et al., (2008) reported no significant difference in the peak force generated within the tendon or in the tendon length when comparing eccentric (tendon lengthening under tension) and concentric loading (shortening under tension) exercises on the Achilles tendon but found high frequency variations in the tendon force during the eccentric exercises. This was suggested as a possible therapeutic effect similar to that seen in bone remodelling where the frequency of loading rather than the magnitude of the force exerted is considered the major therapeutic factor. Other therapeutic effects of eccentric loading reported include normalisation of tendon structures, decreased thickening of the tendon and reduced neovascularisation (Ohberg et al., 2002).

The eccentric loading programme developed by Alfredson et al., (1998) and the one currently preferred in practice is long (12 weeks), laborious (twice a day 7 days per week) and painful to perform. It has been shown to be more effective than the programme developed by Standish et al., (1986) which is carried out over the same duration but consists of both eccentric and static stretching exercises (Stasinopoulos and Manias 2013). Failure to respond to eccentric loading results in continued pain and discomfort which can be debilitating and affect an individual's ability to return to sport or work in occupations which are physical demanding. In these patients, treatment is usually escalated to some form of surgical intervention. With surgical complications at between 11-19% (Paavola et al., 2000 and Paavola et al., 2002) and with the necessity for a long rehabilitation period, the consideration of an alternative non-surgical option to eccentric loading is desirable.

A systematic review of injection therapies using plasma rich protein, hydrocortisone, and sclerosing agents identified poor methodological rigour and inconclusive evidence for their mechanism of action (Gross et al., 2013). In addition to those injections evaluated by Gross et al., (2013), the use of high-volume ultrasound guided injections (HVUGI) has also gained some

popularity as an alternative treatment option for non-insertional Achilles tendinopathy. This intervention involves injecting a large volume (40ml) of injectable saline around the Achilles tendon using ultrasound guidance (to position where the saline is injected). As injectable saline is an inert isotonic substance (having a similar concentration to body fluid) then the risk of adverse reactions should be considerably less than other pharmaceutical agents injected around a painful Achilles tendon.

Several studies have reported on the use of HVUGI for non-insertional Achilles tendinopathy. Although, these studies are constructively appraised and discussed in chapter 4, highlighting some key issues at this stage is considered important in contextualising the reasons for this thesis. All the studies reviewed reported reduced pain and improved function with the administration of HVUGI's, which at face value makes it appear a viable alternative to eccentric loading exercises in patients who may find these difficult to perform.   It could also be considered as an alternative to escalating to surgical intervention where eccentric loading exercises have failed to reduce pain to an acceptable level.   However, apart from one study (Boesen et al., 2019), all studies reviewed adopted a case series approach using patients already under the clinical care of the authors (Chan et al., 2008, Humphrey et al., 2009, Resteghini and Yeoh 2012, Maffulli et al., 2013, Wheeler 2014 Gronbech-Nielson et al 2020). Boesen et al., (2019), by contrast, carried out a two arm RCT comparing the effect of HVUGI's with and without the addition of corticosteroid. In all the studies there was a predominance of participants who were physically active and regularly taking part in sport prior to injury. All had previously received non-surgical treatment which had failed to reduce symptoms to an acceptable level at the time the HVUGI was administered raising the possibility that individuals could experience some delayed long-term effects from the previous treatment, or some as yet poorly understood interaction effect.

The case series approach adopted in all but one of the studies reviewed raises the issue of selection bias as a methodological weakness. Recruiting participants from a similar sporting population challenges the external validity of the findings and their applicability to the general population.   The lack of a control group is considered a weakness in this type of study design as it does not eliminate the effect of any extraneous variables not eliminated by appropriately selected inclusion and exclusion criteria which could have a confounding effect on the results. These confounding effects makes it difficult to ascertain with any confidence whether the reduction in symptoms is due to the administration of the HVUGI. In addition, the constituent components of the injectable solutions varied between studies raising the possibility of

cointerventional bias due to concomitant therapies. Apart from Wheeler (2014) who injected saline plus local anaesthetic, other studies used a mixture of injectable saline, local anaesthetic and some other pharmacological agent including corticosteroid and Aprotinin. As previously intimated studies have shown that the use of hydrocortisone can reduce localised inflammation around the tendon and may well reduce symptoms if administered in isolation but can increase the risk of subsequent rupture. It is this increase in the risk of rupture which has resulted in withdrawal of the use of hydrocortisone in non-insertional Achilles tendinopathy. The local administration of Aprotinin inhibits the effect of collagenase (an enzyme) which has been found to be increased in Achilles tendinopathy and thought to be responsible for the breakdown of collagen, a structural component of the tendon (Maffulli et al., 2013). However, Aprotinin is not licensed for use in the UK and as such cannot be used clinically for tendinopathy. Therefore, evaluating the effect of HVUGI which consists of only saline and local anaesthetic is imperative in the decision to continue its use as an alternative to eccentric loading exercises. The addition of a local anaesthetic agent in all the studies was used to reduce any immediate post-injection pain and discomfort and would not be expected to have any other treatment function or have any effect on pain (other than short term post injection) and function.

In addition to the variations in the pharmacological make-up of the high-volume injection used, Chan et al., (2008), and Resteghina and Yeoh (2012) also instigated an eccentric exercise plan to be carried out following the administration of the HVUGI. The introduction of another intervention known to reduce symptoms and improve function in patients with non-insertional Achilles tendinopathy (Mafi et al 2001) again raises the issue of co-interventional bias.

Although the findings of the studies evaluating HVUGI are at face value encouraging, the methodological weaknesses of a case series approach and the failure to control both the external and internal validity challenge if the results were due to the injection of a high volume of saline or some other confounding variable and as such question if the reported finding would be applicable to the general population Therefore, it is important that any future work endeavours to address these methodological issues by reducing/eliminating variables which might influence the outcome. The use of a safe injectable solution as an alternative to surgery or the eccentric loading programme currently used may be a useful adjunct for the clinician dealing with patients with non-insertional Achilles tendinopathy and facilitate early symptom reduction and return to activity. However, robust evidence from RCTs are required before any evidencebased recommendations could be made promoting the use of saline only HGUVI.

1.1 Professional Context

The PI (Principal Investigator) is a podiatrist registered with the Health and Care Professions Council (HCPC). He qualified in 1997 and has since held several clinical and academic roles. In his role as an Extended Scope Podiatrist within an orthopaedic foot and ankle team he regularly sees patients with non-insertional Achilles tendinopathy. These referrals are primarily from general practitioners but also from podiatrists and physiotherapists working in primary care. The NHS board in which the team is based utilises a series of clinical pathways for common foot and ankle pathologies which includes non-insertional Achilles tendinopathy. These pathways include both diagnosis and treatment algorithms. Eccentric loading exercises are considered as the mainstay of non-surgical management alongside modifications to activity and acute treatment of symptoms. In reviewing patients who have been prescribed eccentric loading exercises it appears that adherence to the exercise programme is varied and some patients report being unable to perform these exercises. Unfortunately, if these exercises fail to improve symptoms to an acceptable level and facilitate return to activity, then the treatment algorithm from this point is vague and includes both surgical and non-surgical options. HVUGI's are one such treatment offered within the NHS Board. However, these are carried out in the department of radiology by several different radiologists who utilise different methodological approaches (variation in the amount of saline injected). In addition, follow up by the foot and ankle team is variable with some patients lost to follow up, some seen by other members of the team and some listed for surgery. Therefore our understanding of their effectiveness as a non- surgical treatment option is unknown locally and as a consequence the value of their use both economically and from the patient's perspective is difficult to justify.

As we emerge from the pandemic the numbers of people waiting for NHS treatment is at a record high with potential for that number to increase further, as people regain confidence in accessing care as the Covid-19 restrictions are eased. However, over the last two years very little elective surgery has been carried out with most health board's still working at a reduced capacity. The NHS recovery plan published by the Scottish Government in August 2021 acknowledged the impact of the pandemic on health and care service and set out the plans for increasing NHS capacity over the five year period between 2021-2026. In an attempt to address the backlog the aim is to increase outpatient capacity by 10% compared to pre-pandemic levels of activity. Although there is additional funding available it is anticipated that the majority of

the increase will be delivered through the redesign of care pathways. Therefore the use of nonsurgical treatment options will be a cornerstone of increasing capacity and reducing the backlog and the numbers of patients being listed for surgery. However, it is important that treatment options provide satisfactory outcomes for patients in order that they can be discharged and able to return to physical activity whether that be recreational or work related.

Even before the pandemic an alternative to eccentric loading exercises for the treatment of noninsertional Achilles tendinopathy was considered a useful option rather than listing patients for surgery. Although HVUGI are offered locally the effectiveness of them compared with eccentric loading as an alternative non-surgical treatment options is unknown but could offer a viable alternative. However, the decision on treatment choice should be based on the best available evidence. As the research literature pertaining to HVUGI is based on poor methodological rigour then a study which would address this knowledge gap provided the stimulus for this study.

1.2 Study design

The review of the literature pertaining to the use of HVUGI identified poor methodological rigour which challenged the internal and external validity of the studies. Therefore, the aim of any future research   should be the development of a methodological approach which should focus on increasing the internal and external validity by addressing some of the weaknesses highlighted in the previous studies. Only by adopting an approach which can prove internal validity will we be able to conclude with any confidence how effective HVUGI is as a treatment. An RCT is internally valid when the design and conduct eliminates bias, and externally valid, but also clinically useful when the result is relevant to a particular group in a particular clinical setting.

According to Altman (2002) a RCT is the methodological approach to use if one wishes to compare groups that only differ with respect to their treatment. He suggested that such trials are conducted prospectively to avoid bias created when comparing treatments carried out at different times and under different conditions. The RCT is considered the most rigorous method to determine the effect of an intervention and is based on the principle of random allocation that is unbiased and as such reduces the effect of any cofounding variables within the sample population by sharing them across the intervention and control groups (Roberts and Torgerson 1998).

Therefore, considering the need to address the weaknesses highlighted when reviewing the current literature pertaining to the effectiveness of HVUGI a properly conducted RCT would seem to address many of the issues and increase the internal validity. However, RCTs can be costly and time consuming to carry out with many not recruiting enough subjects or able to retain them throughout the duration of the study. Consequently, the Medical Research Council guidelines for complex interventions recommends that as part of the planning and development process for an RCT some feasibility work is conducted to demonstrate if the study can be done using the chosen methodology. It is the finding of this feasibility stage of the planning process which is discussed and reported in this thesis and how it might inform any future trials. The rationale for carrying out a feasibility study as part of the planning process is discussed in more detail in section 1.3

The introduction of a control group treated with the usual treatment (eccentric loading exercise programme) currently used in practice, and random allocation of subjects to either the control or treatment group, aimed to eliminate any cofounding effects and reduce selection bias which was identified as a methodological weakness and threat to the internal validity of the earlier studies which have reported on the use of HVUGI. Recruitment was based on a set of clearly defined inclusion and exclusion criteria. The inclusion criteria were key features of the target population whilst exclusion criteria helped minimise random error, selection bias and confounding.

1.3 Rationale for carrying out a feasibility study

Before embarking on an RCT it is important that the researchers are confident that they can recruit enough subjects and retain them throughout the study to ensure that meaningful conclusions can be drawn. Prior to conducting an RCT, the Medical Research Council guidance document for complex interventions (Craig et al., 2008) suggests that pilot/feasibility work should be carried out to assess recruitment/retention, randomisation methods, patient perceptions and compliance and suitability of the intended outcome measures. The purpose of pilot/feasibility work is to reduce the odds of a future trial not proving effectiveness and translation into clinical practice. Although these MRC guidelines continue to be used a new framework for developing and evaluating complex interventions has been commissioned by the National Institute of Health Research and the MRC (Skivington et al., 2021) which not only takes account of how effective an intervention is but also how transferable the results are from the trial into practice, and whether the intervention is cost effective. Evaluating feasibility

continues to be a key component of the planning phase in both the MRC guidelines published in 2008 and the new framework guidelines published in 2021 and will continue to provide supporting evidence to research funding bodies that a large RCT could be carried out utilising the method adopted in the proposed feasibility study. However, this thesis and its associated design and data collection took place in 2020-2021 and therefore the additional elements of the MRC Framework will be considered within the discussion section.

1.4 Definition of feasibility study as applied in this study

The definition used to define the parameters of this feasibility study were based on the guidance provided by the Consolidated Standards of Reporting Trials (CONSORT) (2010) and reported by Eldridge et al., (2016). The guidance focuses on whether a future trial can be done, should be done and if so how. Consequently, the primary aims of this study were to consider if a future RCT could and should be carried out, considering aspects such as recruitment and retention of participants. Several secondary aims tested the data collection and analysis techniques employed using data from a small-scale version of the proposed definitive RCT. However, it is important to note that no hypothesis testing was carried out as part of the analysis of the data, although patterns in the results were noted and reported on in chapter 6.

1.5   Aims and Objectives

1.5.1 Aims

The aim of this study was to assess the feasibility of conducting a future definitive randomised control trial to compare HVUGI with eccentric loading exercises in reducing pain and improving function in subjects with non-insertional Achilles tendinopathy.

1.5.2 Primary objectives

The primary objectives were developed to assess the feasibility of study processes including rates of participant recruitment, retention, and safety whilst also evaluating the outcome measures used in the study and adherence to the eccentric loading exercise programme.

1.5.3 Secondary objectives

The secondary objectives were developed to explore trends in treatment effect, comparing the effect of HVUGI verses eccentric loading on pain and function, tendon thickness and neovascularity in subjects with non-insertional Achilles tendinopathy.

1.5.4 Hypothesis testing

No hypothesis testing was carried out as part of this feasibility study as recruitment rates were part of the primary outcome measures and will help inform the sample size needed to carry out a larger scale study suitable powered to 0.8 with a level of significance of $p \leq 0.05$.

1.6 Overview of thesis structure and chapter content

Chapter 2

The aim of this chapter is to provide a review of the normal structure and function of the Achilles tendon. The chapter begins with a review of the gross anatomy of the Achilles tendon and the associated structures before considering the microstructure of the tendon itself. It will consider function in the context of the normal gait cycle and the load generated through the tendon during each phase of the cycle.

Chapter 3

The focus of this chapter is on the three key areas of epidemiology, aetiology and pathology of non-insertional Achilles tendinopathy. It is envisaged that discussing the epidemiology will give some sense of scale whilst aetiology will provide some explanation to the pathological changes seen in tendinopathy

Chapter 4

This chapter will consider the patient reported outcomes measured in the interventional studies reviewed before providing a critical review of the treatment interventions utilised in the management of non-insertional Achilles tendinopathy and the associated physiological changes that occur. Although a general overview of different treatment interventions is provided the focus is a critical review of HVUGI (treatment intervention) and eccentric loading exercise programmes (control intervention).

Chapter 5

The focus of this chapter is the main experimental phase of this study and discusses how the developed protocol was applied in practice. It includes areas such as the ethical approval process, screening, recruitment, and randomisation. Detailed descriptions are also provided of the process adopted in administering the HVUGI and how the exercises which form the

eccentric loading exercise plan are performed. The process of ultrasound scanning, and the application of the Patient Reported Outcome Measure (PROM) s also discussed.

Chapter 6

This chapter provides the statistical analysis for the data collected in investigating the primary and secondary outcomes of the study.

Chapter 7

This chapter will discuss the results of the statistical analysis carried out in chapter 6 and will view the results in the context of current literature pertaining to the feasibility of carrying out a future RCT to investigate the effectiveness of HVUGI in the treatment of non-insertional Achilles tendinopathy. It also considers limitations of the study and makes recommendations for progression towards carrying out an RCT.

Chapter 8

This chapter provides a summary and conclusions from the experimental work carried in this feasibility study, alongside highlighting areas for future research which this study has identified. In addition, it will discuss how the findings of this study will be disseminated including reference to a draft research paper for submission to a peer reviewed journal

CHAPTER 2 STRUCTURE AND FUNCTION OF THE ACHILLES TENDON

2.1 Introduction to the chapter

This chapter will review the normal structure and function of the Achilles tendon. This overview of the normal anatomy of the Achilles tendon and the forces exerted on it during physical activity will provide an understanding of the mechanisms by which the Achilles tendon works normally, can be injured and how repair might occur. The chapter begins by providing a brief anatomical description of the Achilles tendon and the associated musculoskeletal structures that transfer load through the tendon. The focus will then turn to the microstructure of the tendon and how the structure responds to forces exerted on it when the tendon is loaded.

2.2 Structure and function of the Achilles tendon

The Achilles tendon is the strongest and thickest tendon in the body and is the conjoint tendon of the gastrocnemius and soleus muscles (Cheng Tan and Chan 2008). It is located in the posterior aspect of the lower leg (the 'calf') and is the structural link between these muscles and the calcaneus (heel bone) (Figure 2.1). It facilitates movement around the ankle and knee joint by transmitting the forces resulting from contraction of the gastrocnemius and soleus. The gastrocnemius and soleus are two of three muscles, which makes up the group of muscles referred to in the literature as the triceps surae (Palastanga et al 2006). The triceps surae along with the Achilles tendon makes up the superficial posterior compartment of the lower leg.

The third muscle of the triceps surae is the plantaris, a muscle that, although weaker, has a similar function to that of the gastrocnemius with contraction of the muscle bringing about flexion (extension) of the knee and plantarflexion of the ankle joint (the movement in which the top of the foot points away from the leg). The literature suggests that the plantaris muscle is absent in some people. Daseler and Anson (1943) reported an absence of the plantaris muscle in 6.6% (n=50) of 750 cadaveric specimens with one third of those 50 having a bilateral absence. More recent studies have reported plantaris absence rates of closer to 10%. Simpson (1991) reported an absence rate of 9% when using diagnostic ultrasound to locate and identify the muscle and tendon of plantaris. However, this was based on a small sample size of only 25 patients in the USA (United States of America). This concurs with a study carried out by Olewnik et al (2018) who reported an absence rate of 10.8% following the anatomic dissection of 130 cadaveric lower limbs. As the plantaris muscle has a similar action to that of the gastrocnemius individuals where the muscle is absent can still function in all circumstances.

2.3 Gross anatomy of the Achilles tendon

2.3.1 Achilles tendon

Gastrocnemius

Soleus

Fibres of soleus

Achilles tendon

Calcaneus (insertion of the Achilles tendon)

Figure 2.1 A Posterior lateral view of the Achilles tendon from its origin to insertion on the posterior aspect of the calcaneus (Complete Anatomy 2020).

The Achilles tendon (Figure 2.1) is not a consistent shape and thickness and varies along its length. At its origin it is wide and flat, becoming thinner and more rounded in the mid-section (4cm-6cm from insertion into the calcaneus) before expanding in preparation for inserting into the posterior aspect of the calcaneus. It is this mid-section where the swelling and tenderness is often seen in non-insertional Achilles tendinopathy.

Jerome et al (2010) reported that the Achilles tendon is 12-15 cm long with an average thickness of 6cm. However, some variation in these mean values exist in the literature. Apaydin et al., (2009), in a study which examined 44 lower extremities from 22 adult cadavers (14 males /8 females) with an average age of 63 years (range 45 years to 82 years), found the mean length of the Achilles tendon to be 18.2cm (range 14cm – 24.5cm) with a mean width of 3.4cm (range 2.0cm-4.8cm) at its insertion narrowing to a mean width of 1.8cm (range 1.2cm-2.6cm) at the mid portion section. The range of mean values reported is understandable considering the

variation in the morphology of individuals and as such the size of the Achilles tendon is influenced by race, gender, and age. These influences were studied by Patel and Labib (2018) who carried out an anthropometric mapping exercise of the Achilles tendons of 50 healthy subjects (29 females and 21 males) with an average age of 34.1 standard deviation of 8.8 years, and with no history of Achilles tendon pathology. The study compared tendon length thickness and cross-sectional area between subjects, as well as comparing the dominant and nondominant legs, gender (male and female) and race (black and white). The measurements were performed using diagnostic ultrasound and reported significant variation in Achilles tendon anatomy in the healthy adult population. They found that for all Achilles tendon parameters male tendons were significantly larger with the most significant measurement being the crosssectional area which was 30% larger than in females. These parameters correlated with the difference in height and bodyweight, with males in the study being on average taller and heavier than their female counterparts. However, no significant difference was found between the dominant and non-dominant leg in either males or females in the study.

Although some variations have been reported between studies it is important to acknowledge these variations may have been influenced by different methods of measurements used. Additionally, the tendon measurements from in vitro studies may have been affected by some deterioration of cadaveric specimens. This deterioration was reported by Hohmann et al., (2019) who noted similar load to failure of fresh frozen or preserved specimens but found increased tendon stiffness in those tendons chemically preserved. However, it is unclear from the literature whether the size of tendons is affected by the way in which the cadaveric specimens were preserved, although reduced water content might cause some reduction in size.

As previously stated, the Achilles tendon is the confluence tendon of the gastrocnemius and soleus muscles (Figure 2.1). The tendinous components of the gastrocnemius and the soleus muscles fuse to form the Achilles tendon. The relative contribution of each muscle to the formation of the Achilles tendon is considered to vary between individuals. A classic study by Cummins et al., (1946) estimated the varying contribution of each muscle to the formation of the Achilles tendon. These estimations were calculated from measurements taken from cadavers. Cummins and his colleagues did acknowledge difficulties of measurement due to changing orientation of the tendon fibres, which spiral along the course of the tendon. Of the 100 cadaver tendons measured, Cummins and his colleagues found that in 52 cases the soleus contributed 52% of the fibres and the gastrocnemius 48%, in 35 cases there was equal contribution and in 13 the gastrocnemius contributed more than 60%. At the insertion point on

the calcaneus the Achilles tendon merges with the periosteum, covering the posterior aspect of the calcaneus and at its origin with the fascial membrane covering the muscles of gastrocnemius and soleus. The insertion point on the calcaneus is crescent shaped with significant medial and lateral projections. These projections are thought to aid the dissipation of any stress developed in the tendon being transferred to the calcaneus.

Structurally the Achilles tendon is composed of connective tissue, which consists of tightly packed collagen fibre bundles. They are arranged in such a way as to facilitate the transfer of tensile loads from the gastrocnemius and soleus to the calcaneus. Although the Achilles tendon runs vertically the fibres do not align vertically but instead spiral by 90 degrees with the medial fibres rotating posteriorly and the posterior fibres rotating laterally. From a biomechanical perspective, the spiralling is thought to produce an area of stress with some associated constriction of the vascular supply which might be responsible for the reported avascular zone. In a study utilising Magnetic Resonance Imaging (MRI), the avascular zone was identified about 4cm from the insertion of the tendon into the calcaneus (Jerome et al 2010) which could be a result of the orientation of the tendon fibres and the wringing effect reducing blood flow.

Although this spiralling can be seen as an inherent weakness in the tendon, the orientation of the fibres provides some structural benefits in the form of less buckling when the tendon is lax and reduced deformation of individual strands when under tension. It is also thought to aid in elastic recoil of the tendon (Palastanga 1989). The Achilles tendon, unlike other tendons around the ankle joint, does not have a tendon sheath but is instead surrounded by a paratenon. Although like a tendon sheath, functionally the paratenon differs as it has no synovial membrane (specialized connective tissue that lines the cavities of joints), allows more gliding of the tendon and provides the Achilles tendon with a rich blood supply.

2.4 The microstructure of the Achilles tendon

As previously stated, the insertion of the Achilles tendon merges with the periosteum covering the posterior aspect of the calcaneus and at its origin merges with the fascia covering the muscle. It is the structure of the tendon which makes it possible to transmit large forces from the gastrocnemius and soleus muscle to the calcaneus. The tendon structure is a multi-unit hierarchical structure as illustrated in figure 2.2. It has an Extra Cellular Matrix (ECM) which is composed predominantly of type I collagen, which accounts for 60–85% of the dry weight.

In addition to type 1 collagen the tendon contains other types of collagen including type III, which forms rapid cross-links when a tendon is torn, type V which controls collagen fibril diameter, and type XII which provides lubrication between the fibres (Wang and Guo 2012). The type 1 collagen forms fibre-like structures, which are arranged in a hierarchical order. Each of the structures are aligned close to the long axis of the tissue, in line with the load generated by the gastrocnemius and soleus. This structural arrangement provides excellent uniaxial mechanical strength to the tendon and forms a highly adapted connective tissue which can transfer large loads from the gastrocnemius and soleus muscles to the calcaneus.

Figure 2.2 an illustration of the general hierarchical structure of a tendon (Kastelic et al., 1978).

Figure 2.2 illustrates the hierarchical structure of the tendon showing the smallest structural unit to be the fibril which consists of collagen molecules aligned end to end. These fibrils are bundled together to form collagen fibres which in turn are bundled together to form fascicles. These fascicles are separated from each other by endotendon. The endotendon is a thin layer of connective tissue that contains blood and lymphatics vessel along with nerves (Kastelic et al 1978). Although the collagen molecules are aligned end-to-end there are also cross-links between collagen molecules, which are thought to increase the Young's Modulus of the tendon and reduces its strain at failure (Thompson and Czernuszka 1995). Interspersed between the collagen units are a variety of other non-collagenous matrix components. The non-collagenous proteins can be grouped into proteoglycans, glycoproteins, and glycoconjugates. Proteoglycans

(PGs) are generally divided into large aggregating PGs and Small Leucine-Rich Proteoglycan (SLRP). Large aggregating PGs such as versican and aggrecan increase water content in the tendon providing resistance to compression. SLRPs are the most abundant proteoglycans in tendons, with decorin accounting for roughly 80% of the total proteoglycan content of the tissue (Samiric et al 2004). Its function is to maintain tendon integrity at the molecular level.

There are several glycoproteins contained within the extra cellular matrix of the tendon, which include tenascin-C, fibronectin, lucricin and elastin (Screen et al 2015). These glycoproteins according to Wang and Guo (2012) enhance mechanical stability, facilitate tendon healing and help the tendon return to its pre-stretched length after loading. This recoil or returning to the pre-stretch length is according to Screen et al (2015) facilitated by the elastin and lucrinin that are localised in the matrix between the fascicles.

The cell populations in tendons are poorly defined but are important for tendon metabolism and cellular homeostasis. Unlike the cells found in bone tissue, tenocyte function is poorly understood but two distinct cell populations have been identified and their locations are illustrated in figure 2.2. The tenocytes identified within the fascicles are specialised fibroblasts, which synthesise the collagen rich ECM. Those found in the inter-fascicular matrix appear to be more metabolically active than other cells identified in the ECM. However, it is not clear in the literature what influence this increased metabolism has and what overall effect this has on tendon function. What has been shown in the literature, however, is that tendon cells respond to altered mechanical load. In a study on the patella tendon Miller et al (2005) found that collagen synthesis increased by 100% in a single episode of acute exercise and the increased synthesis was evident some three days later. This influence of loading and exercise will be explored in more detail in chapter 3 when the pathological changes associated with Achilles tendinopathy are discussed.

2.5 Mechanical loading of the Achilles tendon

2.5.1 Loading of the Achilles tendon during the gait cycle

The Achilles tendon is considered an energy storing tendon and is subject to significant forces during loading activities such as walking, running and jumping. Wren et al. (2001) reported peak forces of 9 kilonewtons (kN) (12.5 times body weight) being generated when running at full speed and 2.6kN during slow walking. The gait cycle which describes the sequence of movements during locomotion consists of two main phases a stance phase (60% gait cycle) and

a swing phase (40% gait cycle). The stance phase can be further sub-divided into initial contact, midstance and terminal / pre-swing phases. The gait cycle is illustrated in figure 2.3 and shows that the Achilles tendon is loaded during the stance phase and is responsible for decelerating the rate of dorsiflexion during late midstance whilst bringing about plantarflexion of the foot during the terminal stance phase (e.g. standing on tiptoes) It is the unique structure of the tendon previously described which allows the forces generated in the muscles to be transferred to the calcaneus.

Figure 2.3 The normal gait cycle – the muscles activated at different stages of the cycle are shown in red. (Al-Shuka et al., 2019).

The mechanical behaviour of the tendon when loaded is reflected in the stress-strain curve illustrated in figure 2.4 and described later in section 2.5.2.

2.5.2 The stress strain curve associated with tendon loading

Figure 2.4 illustrates the typical stress strain curve for loading of the Achilles tendon (Korhonen and Saarakkala 2011).

The stress-strain curve (figure 2.4) is a graphical illustration of the reaction of a material (in this case the Achilles tendon) when a load is applied. The stress-strain curve is divided into three distinct regions. These regions reflect the effect on the tendon when the load is increased. In the context of the stress-strain curve, stress refers to the internal forces that resist the applied load whilst strain is the deformation of the tendon because of the external force.

The toe region reflects the initial loading from rest and represents stretching of the tendon by approximately 2%. This stretching can be a result of any activity which loads the Achilles tendon such as walking and running. The wavy or crimped configuration of the collagen fibres at rest are lost as the tendon is loaded and stretched. As the strain on the tendon increases the collagen fibres show a linear response to increasing strain and fibres deform (which conforms to Hooke's law stating that the strain is proportional to the applied stress within the elastic limit of an object). This linear fibre response relates to the elastic region on the stress-strain curve. If strain is less than 4%, the tendon will return to its original length when unloaded. The slope of the curve in the elastic region represents the Young's modulus, which describes tendon stiffness. Reeves (2006) reported a reduced tendon stiffness in older adults (69-80 years) compared with younger adults (20-26 years) and a subsequent reduction in Young's modulus when the tendon stiffness was normalised to the dimensions of the tendons measured in the study. The study also found that the reduced stiffness and subsequent elongation of the tendon

in older adults occurred when a much lower force was generated in the tendon than that applied by younger adults.

If the stress does not exceed the elastic region, then the Achilles tendon should be able to transfer load between the gastrocnemius / soleus and the calcaneus without any damage or trauma to the tendon. However, if the stress exceeds the elastic limit but is less than the failure point, the tendon will not return to its original position and collagen fibre crosslinks will begin to fail. The region between the yield and failure points is referred to as the plastic region. If the strain is maintained between the failure and yield points, microscopic rupture occurs resulting in the symptoms of pain during loading activities.

2.5.3 Viscoelastic properties of the Achilles tendon

The Achilles tendon also displays viscoelastic properties. Viscoelasticity is the property by which the tendon exhibits both elastic and viscous behaviour. These properties are thought to be a result of the interaction between collagen and proteoglycans. This means that a tendon's mechanical behaviour is dependent on the rate of mechanical strain. Therefore, the relationship between stress and strain is not constant but depends on the time of displacement or load (Robi et al 2013). The tendon is therefore more deformable at low strain rates than at high strain rates. Therefore, tendons at low strain rates absorb more mechanical energy but are less effective in carrying mechanical load while at high strain rates the tendon becomes stiffer and therefore more effective in transmitting large muscular loads.

2.6 Summary

This chapter has reviewed the structural anatomy of the Achilles tendon and the stress strain curve. It is important to understand the basic anatomy and process underpinning the normal and abnormal function of the Achilles tendon if we wish to design interventions to treat pain and damage and return function to normal states.

In the next chapter the epidemiology and aetiological factors associated with the development of Achilles tendinopathy are considered and the pathological changes that occur as a result. It is hoped that the review of the literature pertaining to the structure and function of the Achilles tendon in this chapter will help inform our understanding of the pathological changes and how different management strategies work in improving function.

CHAPTER 3 EPIDEMIOLOGY, AETIOLOGY AND PATHOLOGY OF NON-INSERTIONAL ACHILLES TENDINOPATHY

3.1 Introduction to the chapter

This chapter will focus on three key areas of epidemiology, aetiology and the pathological changes associated with the diagnosis of non-insertional Achilles tendinopathy. Discussing the epidemiology will give some sense of scale, whilst the aetiology should provide some explanation to the pathological changes seen in the tendon. However, the chapter will start by considering the terminology used in Achilles tendon injuries and the justification for the use of the term tendinopathy in this study and treatment of Achilles tendon pathology.

3.2 Tendon pathologies and terminologies

3.2.1 Tendonitis

The early descriptions of tendon pathology focused on inflammation of the tendon, in which an inflammatory process led to the pathological changes in the tendon. This was referred to as Tendonitis. The findings of early studies which purported tendonitis was supported by the effectiveness of treatment using anti-inflammatories such as steroids. However, this was challenged by histopathological studies which identified the lack of inflammatory markers (Khan et al., 1999) and therefore influenced the move away from this model and the consideration of other possible causes of tendon pathology. The inflammatory model was revisited by Abate et al., (2009) who suggested that inflammation and degeneration of tendons were not mutually exclusive and that degenerative and inflammatory changes can coexist in adjacent areas of pathological tendon samples. This may well be the reason why antiinflammatory drugs may provide some benefit to patients, if not complete resolution.

3.2.2 Tendinosis

Tendinosis has been defined as degeneration of the tendon without histological signs of inflammation. The collagen fibres of the tendon are disorganised and separated. The affected area of the tendon can also have associated neovascularisation, necrosis and calcification. (Ahmad et al., 2019).

3.2.3 Paratendonitis

Paratendonitis is the result of friction between the tendon and another surface whether that be bone (calcaneus) or footwear which results in inflammation of the paratendon which loosely surrounds the tendon.

3.2.4 Tendinopathy

Irrespective of the histopathological changes in the tendon it is difficult to differentiate clinically between inflammation and degeneration. Therefore, to avoid confusion with the clinical diagnosis of Achilles tendon pathology, and accepting that the clinical presentation can be similar with pain on palpation and loss of function, the term Tendinopathy has been universally accepted both in the research and clinical communities (Maffulli 1998).

3.3 Epidemiology

3.3.1 Incidence of non-insertional Achilles tendinopathy in those who regularly participate in sport

A number of studies have reported on the incidence of non-insertional Achilles tendinopathy in both the athletic (those who regularly participate in sporting activities) and the general population. An early study by Clements et al (1984) reported an annual incidence rate of about 9% in those who participated regularly in sports and activities where running was a major component. This retrospective study was based on patients who attended a sports medicine centre with an overuse type injury of the lower limb. Van Middelkoop et al (2008) investigated the incidence of Achilles tendinopathy in recreational male runners (non-professional runners) registered to take part in the Rotterdam Marathon in 2005. Of the 6000 eligible male runners registered for the race a random sample of 1500 were surveyed using a self- administered questionnaire at baseline (questionnaire returned before the race) and then again immediately after the race. Of the sample surveyed 48.4% (n=725) completed and returned the baseline questionnaire of which 95.7% (n=694) completed the questionnaire post-race. Only subjects where there were baseline and post-race data were included in the analysis. Of the 694 runners surveyed 108 reported a lower limb injury when questioned at baseline and 118 when surveyed again post-race. The incidence of non-insertional Achilles tendinopathy was found to be around 7.4% (n=8) at baseline and 7.6% (n=9) of runners post-race. This study had a number of limitations including the exclusion of females from the sample due to miscommunication

between researchers and organisers, reliance on participants accurately completing the questionnaire and the proportion of those participants lost to follow-up and not included in the analysis.

In a more recent study Lagas et al., (2019) reported on the incidence of Achilles tendinopathy in recreational runners. Although this term is used by the authors there is no definition or criteria described. Baseline characteristics of the included runners recruited from three large running events in the Netherlands, with data being collected within two months of the running events, two weeks before the event, one day after and finally one month after the event. From a sample of 2,378 runners, 1,929 runners completed one or more follow up questionnaires (response rate = 81.1%). Of the 1,929 runners 100 reported the onset of Achilles tendinopathy. Of those 100, 53% (n=53) were male with an average age of 41.9 ± 12.1 years, and with an overall incidence rate calculated at 5.2% (n= 100). However, in those who had registered for the marathon distance of 42km, the incidence rate was 7.4% (n=35) which is the same as that incident rate of 7.4% (n=8) of the 108 runners who reported lower limb injuries in the study by Van Middelkoop et al., (2008) prior to the Rotterdam marathon in 2007.

3.3.2 Incidence of non-insertional Achilles tendinopathy in the general population who do not regularly participate in sport

Although, much of the literature focuses on those who participate in sport whether recreationally or professionally, Achilles tendinopathy can also occur in those who are more sedentary and do not regularly participate in sport or other forms of regular physical activity. Sayana and Maffulli (2007) noted that a sizeable proportion of patients presenting to their clinic with Achilles tendon pain was non-athletic and did not participate regularly in physical activity (defined as less than three 20 minutes sessions of exercise per week for 6 months prior to appointment) although they failed to support their findings with any quantitative analysis. De Jonge et al (2011) investigated the incidence of Achilles tendinopathy in the general population by reviewing data from the computerised records of Dutch GPs. The study reviewed the records of 57,725 patients from 20 separate GP practices recruited from different geographical regions across the Netherlands. General Practitioners in the Netherlands use the International Classification of Primary Care Codes (WHO 2015) which shows both the reason for encounter and the body system affected. Unfortunately, there is no separate classification code for Achilles tendinopathy so the research team used diagnosis specific terms to identify cases. The study found an incidence of 2.35 per 1000 registered patients with an average age of 43.4 years.

It is important to acknowledge that general population studies will also include those who regularly participate in sport. However, this reported incidence of non-insertional Achilles tendinopathy was somewhat lower than the overall incidence reported in sporting populations discussed in section 3.3.1. This was highlighted by the authors who suggested that this might be lower than the actual incidence within the Dutch population due to changes in legislation in 2006 which allowed individuals to self-refer to a physiotherapist or sports physician without first visiting their GP. Therefore, to ascertain a more accurate estimate of Achilles tendinopathy in the Dutch population a survey of physiotherapy and sports medicine practices would also need to be conducted.

In a similar study Albers et al., (2016) also investigated the incidence of lower extremity tendinopathy in Dutch general practice. Using a similar approach as De Jong et al., (2011) they used ICPC-2 codes to identify lower limb pathologies. This was then followed by a review of the actual medical records to confirm the specific diagnosis. Their focus was on a group practice with eight general practitioners with a combined caseload of 10,500 patients. The study reported an overall incidence rate of lower extremity tendinopathy to be 10.52 per 1000 patients of which 2.16 per 1000 presented with Achilles tendinopathy. They also reported that the mean age of those presenting with lower limb tendinopathy was older than in the mean age of the practice population (46 years compared with 36 years). It is important to note that this practice was attached to a university and, as such, likely to have had a high proportion of students on their caseload, which may have resulted in a skewed mean age of the practice.

In a more recent study, the prevalence and incidence of lower extremity tendinopathies was investigated in Danish general practice (Reil et al 2019). The study again utilised ICPC-2 to identify cases of lower extremity tendinopathies in a single GP practice in Aalborg, Denmark. The practice consisted of 3 GPs and seven nurses who carried out 8836 consultations in the period of data extraction from January 1st 2015 until December 31st 2016. In the absence of codes for specific lower limb tendinopathies the less specific ICPC -2 L87 which includes nonspecified bursitis, tendinitis and synovitis was used. Utilising the ICPC-2 coding allowed general musculoskeletal pathologies to be identified which were then reviewed to identify the specific cases of lower limb tendinopathies under review. Four hundred and twenty-one patients' files were extracted which included 632 visits. Of those 274 were excluded due to an irrelevant diagnosis. That left 147 prevalent cases (consultations in 2015 and 2016) and 70 incident cases (consultations in 2016). The study concluded that the prevalence rate of lower extremity tendinopathies was 16.6 per 1000 and an incidence rate of 7.7 cases per 1000. Plantar

heel pain and Achilles tendinopathy were the most common reported tendinopathies. Regarding Achilles tendinopathy there were 46 reported cases equating to an incidence rate of 1.7 per 1000 and a prevalence of 5.2 per 1000 registered patients. The mean age of those presenting with Achilles tendinopathy was 49 $\pm$ 17.1 with 46% of those females and 54% males. This study unlike the study of De Jong et al (2011) did not record any association with sporting activity. The finding of these studies concurs with the author's own experience of working in an orthopaedic department of a large teaching hospital in Scotland where many of those presenting with the clinical signs and symptoms of non- insertional Achilles tendinopathy do not regularly participate in sport.

Unfortunately, a search of the literature failed to identify any epidemiological studies which reported on the incidence of Achilles tendinopathy in the UK, although some data is published relating to general musculoskeletal injuries providing some data on the incidence of lower limb injuries in the UK population. As an example, the Health and Safety Executive publish a report each year on the numbers of workers suffering from work related musculoskeletal disorders which includes Achilles tendinopathy. The reporting is based on two sources of data from the annual Labour Force Survey (LFS) which survey's 37000 households in the UK and from a concurrent survey of a network of occupationally trained general practitioners across the UK (THOR-GP). The results of both surveys provide an estimate of the number of workers suffering from work related musculoskeletal disorder in any one year. Although there has been a general downward trend over the last ten years there were still 480000 workers suffering from work related musculoskeletal disorders resulting in 8.9 million working days lost in 2020 (Health and Safety Executive 2020). Unfortunately, the data does not provide specific figures for individual clinical pathologies but categorises them by anatomical region. Consequently, cases of Achilles tendinopathy are included in the 93000 (19%) cases of reported lower limb disorders in 2020. Although, the case numbers were significantly lower than work related upper limb disorders and back pain, the numbers reported still pose a significant economic burden on both the individual and businesses. Overall, the number of work-related musculoskeletal disorders increase with age with the incidence higher in both the 45-54 and 55+ age groups whilst showing no differences in the incidence between males and females.

In a similar survey carried out by the European Agency for Safety and Health the prevalence, economic burden and demographics of work-related musculoskeletal disorders, was estimated across the European Union (EU-OSHA 2019). This estimate was based on figures from the

2015 European Working Conditions Survey which was conducted across the 28 member states (including UK). The report similar to that of the HSE (2020) identified musculoskeletal disorders by anatomical region rather than specific pathology. The survey estimated that in 2015 lower limb musculoskeletal disorders accounted for 29% of all reported musculoskeletal disorders across the European Union. This was higher than the UK survey where lower limb disorders accounted for 19% of all cases. In the European Union survey the overall percentage of workers reporting one or more musculoskeletal disorders in the UK was 52% below the overall average of 58% recorded across the EU. Similarly, both surveys (the HSE 2020) and the EU-OSHA (2019)) reported an increased incidence with advancing age with both showing significant increases in the 40-54 and 55 plus age groups.

Although the overall economic impact of work-related musculoskeletal disorders across the EU was not reported, the report did highlight the estimated costs to the German economy which was estimated at EUR 17.2 billion of production loss equivalent to between 0.5% and 1.0% of gross domestic product (GDP).

In 2015 the Health and Safety Executive estimated that sickness absence cost the UK £14.3 billion. It also estimated that 40% of all sickness absence was due to musculoskeletal disorders which equates to about £5.7 billion. The Chartered Institute of Personnel and Development Health and Wellbeing report published in 2020 identified musculoskeletal disorders as the second most common cause of short-term absence (less than 4 weeks) behind minor illnesses such as coughs and flu and the second most common cause of long-term absence behind mental ill health. Squires et al., (2011) also acknowledged that the longer a person was on Employment and Support Allowances the less likely they would return to work.

Therefore, in the context of this study a treatment intervention which could provide quicker return to activity (e.g. HVUGI) by reducing pain and improving function in those with noninsertional Achilles tendinopathy could reduce the economic burden of long-term physical therapy such as eccentric loading exercises.

3.4 Aetiology of tendon pathology

As with the challenge of understanding the histopathological changes associated with Achilles tendinopathy, so is the challenge of understanding the exact cause. A number of theories exist which aim to provide some explanation to the probable causes. Factors contributing to tendon pathology are also reported in the literature and are classified into intrinsic and extrinsic risk factors. Intrinsic factors include vascular, mechanical and heat exposure. Extrinsic factors

include changes in training patterns, previous injury, poor movement technique, and the intake of certain drugs (Ackerman et al., 2018)

3.5 Theories on aetiology

In considering the theories of tendon pathology it is important to understand that the tendon is not an inert structure but is a living structure that constantly metabolises to ensure a balance between breakdown facilitated by matrix metalloproteinases and the deposition of new collagen fibres. Under normal conditions, the tendon reacts to the stresses applied to it by increasing the number of collagen fibres. However, the reverse occurs during periods of immobilisation when the number of fibres can be seen to decrease (Cook and Purdam 2009). What is not fully understood is what causes this homeostatic balance to be disrupted resulting in the pathological changes seen in Achilles tendinopathy.

3.5.1 Mechanical theory

The mechanical theory suggests that repeated loading within the normal physiological stress limits causes fatigue and eventually leads to tendon failure. The stress-strain curve illustrated in the previous chapter (section 2.5.2) shows the response to increasing strain generated by loading the tendon. Tendons respond linearly with increasing strain up to 4%. Strains between 4-8% are thought to result in microtears to the tendon matrix, whilst strain above 8% can result in rupture of the tendon. Although the tendon can repair the microtears associated with increased strain, it is usually with the formation of scar tissue which is functionally inferior.

3.5.2 Vascular theory

Tendons are considered to have a poor blood supply, particularly in the mid portion of the tendon, 2-6cm from the insertion into the calcaneus. It is also thought that the stress generated within the tendon during activity causes disruption to the already compromised blood flow resulting in ischaemia. Riley et al., (2004) also reported that the reperfusion of the tendon, which occurs when the stress is released within the tendon, results in the release and exposure to free radicals which damage tendon tissue. Ischaemia can also result from a compromised circulation due to age, trauma, and vascular disease. This theory has however been challenged as some pathological tendons show increased vascularity (Ohberg et al., 2001). However, this could be a healing response to the damaged tendon as neovascularity is considered a diagnostic indicator on Doppler ultrasound investigations.

3.5.3 Over and under stimulation theory

Arnoczky et al., (2007) considered that the damage due to mechanical overloading causes inactivity and subsequently reduced stress on the tendon. This results in under-stimulation of the tendon and may contribute to tendon degeneration. Overloading of the Achilles tendon as postulated in the mechanical theory discussed previously can result in microtears to the tendon structure. The results in the inability to transmit stress and as a result the surrounding tendon becomes under-stimulated due to the structural weakness. According to Ackermann et al., (2018) tendon tissue adheres to the paradigm 'use it or lose it' and that loading is needed to preserve the functioning set point.

3.5.4 Heat Theory

This theory proposes that the heat generated during activity results in the tendon being exposed to increased temperatures that results in prolonged hyperthermia and subsequent tendon tissue damage. However, the invasive nature of direct in vivo measurement using a temperature gauge needle is challenging and not without risk. Therefore, the evidence to support this theory is from either mathematical modelling or animal studies (Jang et al 2019). According to Farris et al. (2011) during running the Achilles tendon stores and returns elastic energy, however the tendon is not perfectly elastic so is unable to return all the energy during recoil. This energy is thus stored as heat within the tendon and results in prolonged hyperthermia. Wilson and Goodship (1994) demonstrated through a combination of mechanical modelling and in vivo measurements that the temperature within the equine superficial digital flexor tendon (SDFT) could reach temperatures of more than 43ºC during galloping. They suggested that this temperature could cause SDFT degeneration. Using mathematical modelling they predicted that similar temperatures could be experienced in the Achilles tendon during running. In a more recent study Farris et al., (2011) utilised mathematical modelling to predict that the core temperature would reach at least 41ºC during running. This predicted temperature was considered conservative but still at a level that could potentially cause tendon damage due to hyperthermia. Although from a theoretical perspective, the theory of hyperthermia resulting in tendon damage would suggest that all physical activity increases the core temperature of the Achilles tendon resulting in injury and it is known from epidemiological studies that this is not the case. As a result, caution should be exercised in considering the heat theory as a single causative factor in Achilles tendinopathy but temperature changes cannot be ruled out as playing some role.

3.6 Risk factors

In addition to the theories of tendon pathology, several risk factors have also been associated with Achilles tendinopathy. These risks factors have been categorised as intrinsic and extrinsic. Some of these risk factors could be considered associated with the theories previously discussed and therefore theories and risk factors could be inter-related and not mutually exclusive. In the following discussion the possible relationship between risk factors and theories is highlighted.

3.7 Intrinsic risk factors

Intrinsic risk factors can include both biomechanical and metabolic disorders which can affect the structure and integrity of the tendon. The biomechanical abnormalities of the lower limb can include abnormal pronation at the subtalor joint, and compensatory movement associated with structural pathologies in the lower limb (Maganaris et al., 2008). The main metabolic disorders reported to be risk factors associated with Achilles tendinopathy include Diabetes, hypercholesterolaemia, obesity and hyperuricaemia (Gout) (Ackermann and Hart 2016).

3.7.1 Diabetes Mellitus

Diabetes is a metabolic disease that results from insufficient production of insulin or peripheral resistance to the action of insulin and is characterised by a chronic state of hyperglycaemia, the result of which leads to severe damage to the heart, blood vessels, eyes, kidneys and nerves over time (WHO 2016). The most common type is type 2 diabetes which occurs when the body develops a resistance to the action of insulin or does not produce sufficient levels of the hormone. Type 1 which usually occurs in the young children or teenagers is where the pancreas produces none or very little insulin.

The relationship between diabetes and tendinopathy was investigated by Ranger et al., (2015), who carried out a systematic review of 31 studies. Of the 31 studies, 26 recruited people with diabetes and five recruited people with tendinopathy. The study found tendinopathy was more prevalent in people with diabetes and diabetes was more prevalent in with tendinopathy. Duration of diagnosis with diabetes was also seen to be a factor with those patients with longer duration of diabetes more likely to suffer with tendinopathy.

A study carried out by Batista et al., (2008) identified structural changes of the Achilles tendon in patients with diabetes. They carried out ultrasound scans on 70 consecutive patients with

diabetes and asymptomatic for Achilles tendinopathy. The study reported that 89% of patients displayed disorganisation of the tendon structure and that 76% displayed some intra-tendinous calcification. These changes were not seen in a small control group of non-diabetic patients (n=10) matched for age and with no previous history of Achilles tendinopathy.

The cause of the structural changes associated with diabetes is thought to be because of the increased synthesis of Advanced Glycation Products (AGE). These form when proteins or fats mix with glucose in the blood. Normally the body synthesises AGEs at a slow, steady pace, however, in patients with diabetes (and the associated elevated levels of circulating glucose) AGE synthesis is accelerated. AGE formation changes the structure of the collagen proteins which make up tendons

In addition to the changes in structure seen in the Achilles tendon resulting from the increased synthesis of AGEs, diabetes is also known to affect the peripheral circulation. Therefore, diabetes could contribute to the Vascular Theory previously discussed by compromising the already poor blood supply to the tendons by the metabolic effects on the macro- and microcirculation in the lower limb resulting from hyperglycaemia.

3.7.2 Hyperlipidaemia

Hyperlipidaemia is defined as an elevation of fasting total cholesterol concentrations which may or may not be associated with raised triglycerides. As lipids are not soluble in plasma they are transported in the blood as lipoprotein complexes (Nelson 2013). Diagnosis of hyperlipidaemia involves measuring the levels of the different circulating lipoproteins in the blood   which can have varying effects on the cardiovascular system. Elevated Low-Density Lipoproteins (LDLs) are considered to be a major risk factor in the development of cardiovascular disease whilst High Density Lipoproteins (HDLs) are considered to provide some cardiovascular protection. Elevated LDLs are considered to be one of the main risk factors associated with the development of atherosclerotic plaques which restrict blood flow in medium and large arteries and a major cause of arterial disease in both coronary and peripheral vessels. The peripheral arterial disease could affect the flow to the Achilles tendon and support the vascular theory discussed previously. In addition, pathological changes have been observed as a direct result of cholesterol accumulating in the Achilles tendon, making it more susceptible to tendinopathy. The accumulation of cholesterol results in thickening of the Achilles tendon referred to as Achilles xanthomatosis (figure 3.1) is more commonly seen in patients with familial hypercholesterolaemia (Abate et al., 2013). The relationship between familial

hypercholesterolaemia, and xanthomas are also considered markers for cardiovascular disease (Oosterveer et al., 2009).

Figure 3.1 Illustration of xanthoma formation resulting from familialhypercholesterolemia. Note the bilateral swelling of both Achilles tendons (Beeharry et al., 2006).

An ultrasonographic study of the Achilles tendon in patients with severe hypercholesterolaemia carried out by Kutkiene et al., (2019) found that Achilles tendinopathy was more prevalent among patients with severe hypercholesterolemia than a control group with normal lipid levels. In this study by Kutkriene et al., (2019), Achilles tendinopathy was diagnosed by evidence of fusiform thickening of the tendon and disruption of the tendon fibres with or without focal intra-tendinous hypoechogenicity using ultrasound. The early diagnosis of xanthomas is thus important, both as a cause of Achilles tendinopathy but also as an early biomarker for hypercholesterolaemia. Unfortunately, in some cases the xanthomas can be too small and thus difficult to detect on ultrasound. However, it is important to note that Achilles xanthomatosis presents as a bilateral uniform thickening of the Achilles tendon, dissimilar to Achilles tendinopathy which often presents unilaterally and has a fusiform thickening some 2-6cm from the insertion (Carranza et al., 1999). These differences in clinical presentation between Achilles xanthomatosis and Achilles tendinopathy are important and key observations both for clinical practice and when designing research studies.

3.7.3 Gout

Gout occurs because of a metabolic inefficiency to metabolise purines resulting in hyperuricemia. These raised levels of uric acid result in the formation of insoluble monosodium urate crystals which can be in joints and tendons. The crystals that form in joints cause acute

attacks of severe pain and swelling. Repeated episodes of gout result in damage to the articular surface of the joint and later the development of secondary osteoarthritis.

Figure 3.2 Ultrasound scan illustrating the formation of multiple tophi because of hyperuricemia associated with gout (Araujo et al., 2016).

The Achilles tendon is also commonly affected by deposits of monosodium urate crystals. The deposition of these crystals results in the formation of subcutaneous bodies called tophi (figure 3.2). These structures found within the tendon disrupt the organisation of the collagen fibres, affecting the mechanical and structural properties of the tendon (Chhana et al., 2014). It is also important to note that in addition to the structural changes associated with the deposition of crystals, an inflammatory response is also initiated which increases the water content resulting in changes to tendon structure and stiffness (elasticity).

3.7.4 Obesity

A person with a Body Mass Index (BMI) greater than 30kg/m² is considered obese and obesity is a risk factor in the development of Type 2 diabetes, hypertension, hyperlipidaemia and atherosclerosis. The pathogenesis of Achilles tendinopathy because of obesity is considered multifactorial with both metabolic and mechanical considerations. As the Achilles tendon is a weight-bearing tendon then the increased BMI increases the load through the tendon and as such could be considered a contributory factor to the Mechanical theory previously discussed. In addition, obesity is associated with several comorbidities including Type 2 Diabetes, Cardiovascular Disease, metabolic syndrome, and some cancers (Pi Sunyer 2009). Again, the

link to Type 2 diabetes, cardiovascular disease and the cardiovascular risk factors associated with metabolic syndrome would be considered a contributory factor to the vascular theory discussed early in section 3.3.2. However, there is a direct metabolic link with obesity and tendinopathy. Adipose tissue is now considered a major endocrine organ and in obese patients the release of bioactive peptides and hormones can result in modification to tendon structures. Alongside the release of peptides and hormones, there are persistently raised prostaglandins E2, leukotriene B4 and Tumour Necrosis Factor alpha in obese patients. This results in a chronic subclinical low-grade inflammation which may affect tendon homeostasis (Cilli et al., 2004, Abate et al., 2016). The altered structure due to the metabolic effects of obesity and the increased load due to the high BMI makes the tendon susceptible to Achilles tendinopathy.

3.7.5. Biomechanical risk factors

As previously discussed, increased load through the tendon because of obesity can create increased strain and subsequent damage to the tendon. In addition, structural pathologies in the lower limb and the associated functional compensation are also considered to affect structure and function of the Achilles tendon and the associated musculature.

Excessive foot pronation which results in eversion of the hind foot is considered a risk factor in the development of Achilles tendinopathy. However, it is important to note that pronation of the subtalor joint is a normal movement during the gait cycle and should occur during the initial contact phase. The pronatory movement is considered essential in absorbing shock from the ground reaction force as the lateral aspect of the heel strikes the ground. It is also unlocks the forefoot and the rearfoot so that the foot is mobile. The mobility of the foot during this initial contact phase not only aids in shock absorption but allows the foot to adapt to any unevenness in the contours of the ground. As the foot progresses through the stance phase of gait shifting from the initial contact phase to the midstance phase and finally into the propulsion phase, the foot will supinate locking the hind foot and forefoot lock thus creating a rigid level for propulsion. Over pronation or abnormal pronation occurs when the foot remains pronated as it transitions from midstance to propulsion. This abnormal pronation occurs because of malignment of the lower limb and the foot, such as tibia varum and forefoot varus. Restricted dorsiflexion (ankle equinus) in the ankle joint is also compensated by abnormal pronation of the subtalor joint.

Figure 3.3 Illustrates the eversion of the hindfoot associated with adult acquired flatfoot.

The abnormal pronation results in an everted hindfoot and alteration in the travel of the fibres of the Achilles tendon. This alteration is thought to result in an impairment in the blood supply. It has been described as having a 'wringing out' effect on the blood vessels supplying the tendon and the prolonged period in the pronated position during the stance phase contributes to what Clements et al., (1984) described as the hypovascularisation, degeneration injury cycle. The effect of pronation on blood flow was investigated by Karzis et al., (2017). Using Doppler ultrasound, the Achilles tendon blood supply was analysed in a relaxed non-weight bearing position and then in both single and double limb support. The study found that over pronation resulted in increased vascular resistance and reduced blood flow at the mid tendon (6cm from the insertion) and at the osteotendinous junction on the calcaneus. The reported reduced blood flow associated with abnormal pronation could be seen as a contributory factor to the vascular theory discussed early in the chapter. Becker et al., (2017) investigated the factors associated with Achilles tendinopathy and Medial Tibial Stress Syndrome in runners. The study found that the injured participants when compared to a matched control group exhibited a higher standing tibia varus angle, reduced static dorsiflexion and longer duration of eversion (Pronation) during the stance phase of gait.

3.8 Extrinsic risk factors

According to Ackermann et al., (2018) extrinsic factors include poor training techniques, previous injury, changes in training patterns, environmental factors and the intake of certain drugs. This concurs with an earlier review by Maffulli et al., (2003) who suggested that the aetiology of Achilles tendinopathy was a combination of intrinsic and extrinsic factors.

Extrinsic factors they identified as training errors (training volume and techniques), training surfaces, and footwear.

Poor training techniques including alterations in training patterns have been implicated in the development of Achilles tendinopathy. In a prospective study carried out by Di Caprio et al., (2010) 166 runners were recruited from three running clubs in Northern Italy. The participants from different running disciplines were followed and examined over a 4-year period and assessed for risk factors associated with the development of several lower limb pathologies including Achilles tendinopathy. Of the 166 runners 86 were male and 80 were female with an average age of 31.1 ± 12.2 years and included both recreational and competitive runners. Non traumatic foot and lower limb pathologies resulting in a minimum rest period of two weeks were recorded over the period of the study. The study evaluated general characteristic of the runners including age, sex, height, weight and BMI along with sport specific characteristics including type of running, level, running surface, footwear, and volume of training. Achilles tendinopathy was reported as the most common injury second only to plantar fasciitis with 24.1% of runners reporting an episode within the 4-year period.

In this study the athlete's age, gender, height, weight and BMI were not statistically related to Achilles tendinopathy. Although it is important to note that the mean age of the cohort was relatively young at 31. 1 years and the average BMI was reported to be within the normal range, there were several risk factors found to be associated with the development of Achilles tendinopathy. The study found Achilles tendinopathy to be more prevalent in competitive runners (29.1%, n=32) than recreational runners (14.3%, n=8) whilst long- and middle-distance runners were affected more than sprinters and hurdlers. With regards to footwear running spikes were strongly linked with the development of Achilles tendinopathy as were shock absorbing shoes when compared to what they referred to as super light shoes and all other running shoes. A multivariate analysis of the data pertaining to volume of training showed that there was statistical significance between years of activity (affected 13.8 ± 7.2 v non affected 8.4 ± 6.5), days of practice per week (Affected 5.6 ± 1.5 v non affected 4.7 ± 1.5) and distance per week (affected 63.5 ± 26.9 km v non effected 42.2 ± 24.1 km).

A similar study carried out by Knobloch et al., (2008) investigated the incidence of Achilles tendinopathy and if the incidence was related to training volume and training surface in masters running athletes. Participants were recruited through an advertisement in a German running magazine and therefore it could be considered a self-selected sample and not representative of the running population which consists of athletes of all abilities and ages. The study found that mid-portion Achilles tendinopathy was more common than insertional Achilles tendinopathy and was the most common overuse injury in the lower limb. Runners with more than a 10-year

running history were significantly more likely to suffer with Achilles tendinopathy than a runner with less. Running surface was also found to be a risk factor with an asphalt surface less likely to cause the condition than running on sand.

A review of the two studies highlighted some limitations in the results. Both exhibited methodological approaches which threatened the internal and external validity of the results. These included a focus on running populations with no use of a comparable control group and failure to control any possible confounding effects of intrinsic factors.

These limitations were further highlighted by O'Neill et al., (2016) who carried out a Delphi study on risk factors in the development of Achilles tendinopathy. Opinions were sought from world tendon experts (criteria for inclusion was the publication of two research articles on Achilles tendinopathy in the prior 10 years). With regards to extrinsic risk factors, they were considered in the context of active/ athletic individuals and inactive / sedentary individuals. The process ranked the extrinsic risk factors for both groups and concluded that in the active/athletic group changes in loading (rapid increase when returning from closed season /holiday), training errors (ramping up training), activity levels, footwear and training surfaces whilst in the inactive /sedentary group changes in loading was ranked highest by the experts followed by activity levels and footwear. A further exploration of what the panel considered as training error in the active / athletic group and activity levels in the inactive / sedentary group was also carried to provide some clarity pertaining to these specific risk factors ranked for each group. Training errors were ranked in the following order: sudden increases in training level were ranked first followed by types of loading (hill work), recent alterations in training, intensity of training, duration of training, frequency of training and weekly training. Again, one could argue that there is significant overlap of the risk factors on this list with many if not all the factors resulting on increased tendon loading

Regarding a ranked breakdown of the risks associated with physical activity in the inactive/sedentary group sudden changes in activity levels was ranked first followed by recent alterations in activity, changes in loading (types of activity, types of activity they take part in, activity level (accumulative time) and finally frequency of activity. The authors thought that the identification of the external risk factors may serve to provide a focus for future empirical research and thus provide a better understanding of the influence of these external risk factors on the development of non-insertional Achilles tendinopathy.

In addition to the external risk factors associated with training techniques and training volume certain drugs have been shown to increase the risk of developing Achilles tendinopathy. Although the use of statins and oral contraceptives have been identified in the literature the evidence is unclear. Statins are used in patients with hypercholesterolaemia (Primary and Familial) where diet and other lifestyle changes have failed to reduce cholesterol levels (BNF). One of the side effects identified is muscle toxicity, resulting in myopathy and tendinopathy. However, it is unclear the level of risk associated with the use of statins. Marie et al., (2008) carried out a retrospective study of cases where statins were linked with tendon complications. The data was collected from 31 French Pharmacovigilance centres. From 1990- 2005 a total of 4597 statin associated global side effects were reported with 96 of those having tendinous manifestation (2.09%) of which 50 (52.1%) involved the Achilles tendon. It is important to note that 27 cases (28.1%) had other comorbidities which are considered risk factors for the development of tendinopathy such as diabetes, physical exertion, hyperuricaemia and a history of tendon disorders. Overall, the study suggested that statin attributed tendinopathies are rare considering the widespread use of statins in the management of cholesterol and its impact on cardiovascular disease. A systematic review carried out by Teichtahl et al., (2016) reported that there is a lack of evidence to implicate statins as a risk factor for tendon rupture but did find that simvastatin reduced the risk of tendinopathy, therefore suggesting a protective rather than a causative effect. This might be expected if one considers that hypercholesterolaemia is a risk factor in the development of Achilles tendinopathy and a reduction in cholesterol levels particularly LDLs would reduce symptoms associated with this known risk factor.

3.9 Summary of the chapter

This chapter has identified that many intrinsic and extrinsic risk factors can predispose a patient to the development of non-insertional Achilles tendinopathy. Intrinsic risk factors include both metabolic and biomechanical disorders whilst extrinsic factors include poor training techniques including changes in physical activity levels and the intake of certain drugs. As a result, the aetiology is a complex interaction of these factors with a single causative factor rare. What was not evident in the literature was that improvement in glycaemic control in patients with diabetes or reduced cholesterol in those with hyperlipidaemia resulted in resolution of symptoms associated with tendinopathy. However, control of these metabolic parameters within the normal range alongside weight control through exercise and diet would aid other treatment interventions which primarily focus on the pathological changes in the tendon.

Although most studies investigating treatment intervention exclude subjects with previous foot and ankle trauma or those with diagnosed rheumatological conditions, they do not exclude those with diabetes, hyperlipidaemia, or obesity and as such were not factored into this feasibility study. It was anticipated in this study that the randomisation process would allow for these metabolic conditions by distributing them across the control and treatment group. However, the review of the literature in this chapter does highlight the possible influence of these metabolic disorders on Achilles tendinopathy and a consideration in any future study. In the next chapter the focus will be the treatment of non-insertional Achilles tendinopathy with particular emphasis of HVUGI which was administered to the treatment group and eccentric loading exercises which were performed by the control group.

CHAPTER 4 OUTCOME MEASURES AND TREATMENT OF NONINSERTIONAL ACHILLES TENDINOPATHY

4.1 Introduction to the chapter

In chapter 3 the epidemiology and aetiology of non- insertional Achilles tendinopathy was discussed along with the physiological changes associated with this common overuse injury. This chapter starts by reviewing the Patient Reported Outcome Measures utilised in the interventional studies reviewed. This will include their application and the validity and reliability of the measurements recorded. Finally, a critical review of the treatment interventions and the associated physiological changes will be discussed. Although a general overview of the different treatment interventions will be presented, the main emphasis will be on a critical review of eccentric loading exercise programmes (experimental control) and HVUGI (treatment intervention).

4.2 Non-surgical interventions used in the management of non-insertional Achilles tendinopathy

A variety of management approaches both non-surgical and surgical have been described in the literature for the treatment of Achilles tendinopathy. Non-surgical approaches include alteration to training or activity patterns, eccentric loading exercises, use of Non-Steroidal Anti-inflammatory Drugs (NSAID), Extracorporeal Shockwave Therapy (EWST) and injection therapy. Studies have reported injecting the tendon with hydrocortisone, plasma rich protein, vascular sclerosing agents as well as ultrasound guided injections of high volumes of saline, sometimes with the addition of small amounts of other drugs such as local anaesthetic, hydrocortisone and Aprotinin (Willberg et al., 2008, Coombes 2010, van Sterkenburg et al 2010, Murawski et al., 2014). The use of hydrocortisone injections has fallen from favour due to the reported increased risk of rupture, subcutaneous atrophy and skin depigmentation (Maffulli et al., 2004). Currently the mainstay of non-surgical treatment is eccentric loading, which displays variable short and long-term results (Mafi et al., 2001, Sayana and Maffulli 2007). The use of NSAID has always been questioned due to the protracted nature of noninsertional Achilles tendinopathy and the lack of inflammatory markers on histopathological examination (Khan et al., 1999). However, the inflammatory model was revisited by Abate et al., (2009) who suggested that inflammation and degeneration can coexist in adjacent areas of the tendon, suggesting anti-inflammatory drugs may provide some benefit (if not complete resolution) in the early stages of the disease process.

However, this was challenged by the study of Malmgaard-Clausen et al., (2021) who conducted an RCT to investigate if NSAID drugs alongside a physical therapy programme would augment the rehabilitation process. Using clear inclusion and exclusion criteria, a random allocation method and blinding of both the participants and the researchers this study demonstrated good methodological rigour. A total of sixty-nine participants were randomised into two groups, one group were prescribed NSAID alongside a physical therapy programme (n=34) whilst the other group received a placebo drug and physical therapy programme (n=35) The study used the VISA-A questionnaire (see Section 4.3) to measure pain and function whilst physiological measurements of tendon thickness and neovascularity were recorded using diagnostic ultrasound. The study found no significant difference between the groups at baseline, one week and at three months. At one week and at three months both groups showed increases in the VISA-A score suggesting improvement in function and reduced pain although no changes in the physiological measurements were found. The authors concluded that the reduced pain and improved function in both groups was the result of the rehabilitation programme and that the NSAID had no added effects on the treatment.

As eccentric loading exercises continue to be the mainstay of non-surgical management, it was considered a suitable control intervention in this study. A detailed review of the literature pertaining to the use of eccentric loading exercise programmes in the management of noninsertion Achilles tendinopathy is discussed in section 4.6.

4.3 Patient Reported Outcome Measures used in the evaluation of treatment interventions for non-insertional Achilles tendinopathy

Patient Reported Outcome Measures (PROMs) are standardised validated questionnaires that are completed by patients to measure their perception of their own functional status and wellbeing (Dawson et al., 2010). They were originally designed for use in pharmacological and health service research to calculate the health gains from treatment interventions but are now used widely to measure the effectiveness of treatment outcomes in clinical practice. They have become mandatory in the UK to report outcomes for certain elective surgical patients as a method of analysing care from a patient's perspective and have helped the NHS identify strengths and weaknesses of the services provided (Weldring and Smith 2013). Some PROMs assess patient perceptions of their general health whilst some are disease specific.

In addition to service evaluation the use of a standardised questionnaire allows comparisons to be drawn between studies using similar treatment interventions as well as allowing the

comparison of treatments for specific clinical pathologies. However, in drawing comparisons, it is important that any PROM provides valid and reliable results.

In reviewing the research literature pertaining to HVUGI, the PROM used in all the studies was the universally accepted VISA-A questionnaire (see 4.3.1 below). However, when reviewing the literature pertaining to eccentric loading a variety of PROMs have been used in its evaluation. The early papers utilised the Visual Analogue Scale (VAS) to report on pain levels, as well as reporting on patient satisfaction, although no specified patient satisfaction tools are reported in the research papers. Satisfaction appeared to be 'return to everyday activity' rather than any other aspect of their clinical care. However, since 2001 the papers reviewed on treatment interventions including eccentric loading have used the VISA-A questionnaire to measure patient outcomes pertaining to pain and function. The adoption of the VISA-A questionnaire since its inception in 2001 has made comparing the effectiveness of treatment interventions for non-insertional Achilles tendinopathy easier.

The validity and reliability of a PROM is important when considering the results for any clinical intervention. It is imperative that any measurements are both reliable (reproducible) and valid (accurate). These are key requirements in ensuring that measurements are consistent and measure what they are supposed to measure. The validity and reliability of the VISA-A questionnaire (consisting of VAS and categorical rating scales) are considered in the following section along with a brief description.

4.3.1 Victoria Institute of Sport Assessment – Achilles (VISA-A)

Since 2001 Achilles tendon studies have utilised the Victoria Institute of Sports Assessment–Achilles (VISA –A) questionnaire as a primary outcome measure (Robinson et al.,2001). It is self-administered and disease specific. The use of a standardised outcome measure is considered useful and allows direct comparisons to be made between studies. The questionnaire itself is an inverted numerical rating scale with a scoring range between 0-100, where an asymptomatic subject would score 100 (Iversen et al., 2012)

It consists of eight questions which use a mix of VAS (Visual Analogue Scales) and categorical rating scales The first 6 questions utilise VASs to measure the magnitude of subjective symptoms, whilst the last two questions utilise categorical rating scales measure activity levels (see appendix 6). The advantage of using VAS include high sensitivity, and applicability across a wide variety of populations, whilst being considered easy to analyse and administer (Kliger

et al., 2015). The use of categorical rating scales for activity and is based on an incremental range of values.

In the development of the VISA-A questionnaire, Robinson et al., (2001) evaluated its validity and reliability. Evaluation of the questionnaire was done by comparing the results from four separate groups which were considered to reflect differing severity of non-insertional Achilles tendinopathy. The four groups included two patient groups (non-surgical patients with Achilles tendinopathy and a group of pre-surgical patients with Achilles tendinopathy), a control group of young active university students and an age-matched, non-injured group of recreational runners. The authors were able to establish construct validity by comparing the mean VISA-A scores of the 4 groups. The VISA-A score was more than 96 (94-99) for the control group (young normal active people) the non-surgical patients scored 64 (59-69) and the pre-surgical patients 44 (28-60). They were also able to show good test-retest reliability ($r = 0.93$), intrarater ($r = 0.9$) and inter-rater ($r = 0.9$) reliability. The sequence of reliability testing used by the authors evaluated the reliability of the questionnaire under different research conditions. The results demonstrated consistency across time and illustrated that reliability was not affected or influenced by the administering researcher.

Inversen et al., (2012) also evaluated the reliability of the VISA-A questionnaire for measuring pain and function in patients with non-insertional Achilles tendinopathy. The systematic review included 26 clinical trials containing 1336 individuals aged 18 years or older with a diagnosis of chronic non-insertional Achilles tendinopathy. The authors found that healthy subjects scored 96 or above and scores of lower than 24 were rarely attained, even in the most severe cases of Achilles tendinopathy. This concurs with the original work carried out by Robinson et al., (2001) regarding the severity of non-insertional Achilles tendinopathy and the VISA-A scores. The study also found that only in a small number of cases the scores posttreatment matched those of uninjured healthy subjects.

Pearson et al., (2012) identified the effect size thresholds as five points for a small effect and 15 points for a moderate effect. Although it is considered a valid and reliable tool for Achilles tendinopathy, ankle sprains and other musculoskeletal conditions of the foot and ankle can affect the overall score and as such could provide a false negative. As an evaluation tool it is only effective in assessing pain and function in isolated cases of Achilles tendinopathy and it is therefore imperative that studies which use the VISA-A questionnaire have clear exclusion criteria which might help eliminate possible false negatives. This was highlighted by Robinson

et al., (2001) who suggested that other lower limb pathologies can reduce a patient's VISA-A score.

4.4 Physiological measurements used in the evaluation of non-surgical treatment interventions for non-insertional Achilles tendinopathy

In addition to the PROMs utilised to evaluate the patient's perception of pain, some physiological markers are also measured including neovascularity and tendon thickness. As discussed in the previous chapter, tendon thickening and the development of new blood vessels around the tendon are two physiological characteristics of non-insertional Achilles tendinopathy and measured in several studies. Therefore, the validity and reliability of these measurements are also presented.

4.4.1 Öhbergs modified neovascularisation Score

Neovascularisation is measured using diagnostic ultrasound and quantified using the Modified Öhberg Neovascularisation Score (table 4.1). The scoring system is a semi-quantitative grading system shown to have excellent inter and intra-rater reliability which is discussed later in the section.Intra-rater reliability refers to consistency of measurement by an individual observer and inter-rater reliability to measurements performed by multiple observers.

Table 4.1 – Illustration of the Modified Ohberg Scores with associated descriptions.

Modified Ohberg Score	Description
0	No vessels

1+	One vessel anterior to the Achilles tendon
2+	Two vessels throughout the tendon
3+	Three vessels throughout the tendon
4+	Four or more vessels throughout the tendon

 A measure of reliability is needed to establish inter and intra class correlation of any measurements recorded. The Modified Ohberg Neovascularity Score has been shown to have excellent inter and intra-rater reliability with an intraclass correlation coefficient (ICC) of 0.85 (Sengkerij et al., 2009). This concurs with a more recent study by Watson et al., (2018) who investigated inter and intra tester reliability of measuring neovascularisation amongst a group of sport and exercise consultants. They found that neovascularity was evident in 65.6% of symptomatic tendons and that the ICC for inter tester and intra tester reliability was 0.86 and 0.95, respectively. Cicchetti (1994) provided guidelines regarding the interpretation of the ICC results and reported that anything between 0.75 and 1.0 was excellent.

4.4.2 Measuring tendon thickness (reliability of measurements)

One of the classic features of Achilles tendinopathy is thickening of Achilles tendon. This usually occurs about 2-6 cm from the insertion of the tendon into the calcaneus. Measurement of tendon thickening is carried out pre and post intervention as it is hypothesised that any thickening reduces with reduction in symptoms. Diagnostic ultrasound is widely utilised in the diagnosis of musculoskeletal pathology and can illustrate thickening of the tendon, neovascularity, and disruption to tendon fibres. However, it is important to ensure that any measurements taken are consistent whether performed by the same observer or multiple observers. Diagnostic ultrasound machines have integrated measurement capacity and this is the method used to evaluate tendon thickness pre and post intervention. Several studies have reviewed the consistency of diagnostic ultrasound measurement using ICC. Dudley-Javoroski et al., (2010) who reported intra tester reliability ranging from 0.76 for a novice operator to 0.92 for an experienced operator. In a systematic review carried out by McAuliffe et al., (2017) inter-tester reliability when measuring tendon thickness was found to be between 0.65 and 0.84. Although intra tester reliability reported by Dudley-Javoroski et al., (2010) was considered

excellent the ICC of 0.92 would suggest that the more experienced the operator the more consistent the measurement.

4.5 Analytical review of the research literature pertaining to High Volume Ultrasound Guided Injections (HVUGI)

As previously reported the clinical signs and symptoms of Achilles tendinopathy are marked thickening of the Achilles tendon some 2-6cm from the insertion into the calcaneus and pain on palpation of the tendon around the thickened portion. Ultrasound evaluation of patients presenting with the classic signs and symptoms of non- insertional Achilles tendinopathy show disruption to the tendon fibres, thickening of the tendon and evidence of neural ingrowths with neovascularisation. Earlier studies carried out by Öhberg and Alfredson (2002), and Alfredson et al., (2007) have shown that sclerosing these neo-vessels is associated with a reduction in pain and improved function. Although the sclerosing agent, polidocanol used in these studies is considered safe it is not licenced for use in the UK and therefore researchers have looked for alternative methods to reduce the neovascularisation associated with Achilles tendinopathy.

The injection of a high volume of injectable saline under ultrasound guidance between the anterior aspect of the Achilles tendon and the Kager's fat pad has been considered as an alternative to injecting a sclerosing agent. Results in the published literature has shown positive results in reducing pain and improving function. A review of the studies which have employed HVUGI in the treatment of Achilles tendinopathy has been carried out and is presented later in this chapter. The aim of the critical analysis below (4.5.1) is to highlight issues of internal and external validity whilst comparing the methodological approaches adopted. The limitations identified in the published literature helped inform the development of the methodological approach adopted in this study and lead to improvements in the validity of future studies pertaining to the administration of HVUGI.

4.5.1 Literature Search Pertaining to High Volume Ultrasound Guided Injections

A comprehensive review of the literature pertaining to the use of HVUGI (treatment intervention in this study) in the treatment of non-insertional Achilles tendinopathy was carried out. This was achieved through a systematic search of the literature between September 2014 and July 2020 employing a PICO strategy. The PICO strategy focuses on four key areas in identifying the components of clinical evidence and includes Population, Intervention, Control,

and Outcome. A number of search terms were used under each heading which are detailed in Table 4.2

The following databases were searched using a text word search.

- CINAHL
- Medline
- SPORTDiscuss
- Scopus
- Cochrane Database of systematic reviews

Table 4.2 PICO template to identify and combine key words used in the electronic search of the literature.

Column treatment combined with OR	Population /Condition AND	Intervention AND	Comparative intervention AND	Outcome AND
OR	1.Achilles tendinopathy	7. Treatment	12.Eccentric loading	18.VISA-A
OR	2.Non – insertional Achilles tendinopathy	8.Injection therapy	13.PRP Injection	19.VAS
OR	3.Mid-portion Achilles tendinopathy	9.High volume saline injection	14.Sclerosing agent	20.Tendon thickness
OR	4.Achilles tendinosis	10.High volume ultrasound guided injection	15.Corticosteriod	21.Neovascularity
OR	5.Achilles tendonitis		16.Autologous blood injection	
	6 Combine 1-5 using OR	11 Combine 7-10 using OR	17 Combine 12-16 using OR	22 Combine 18-21 using OR

In each column are key words used to describe each column heading. These key words in each column are combined by using OR. This finds citations containing any of the keywords. The columns are then combined using AND which finds citations that contain all the specified terms. This method was repeated for searching each database.

4.5.2 HVUGI for the treatment of non-insertional Achilles tendinopathy

The literature search utilising the search terms and method detailed in the PICO table identified seven research papers published between 2008 and 2020 which investigated the effect of HGUVI on subjects with Achilles tendinopathy. No studies prior to 2008 were found using the above systematic approach. The studies identified in the search are detailed in the table in appendix 7.

Of the seven studies identified in the search there was only one RCT (Boesen et al., 2019) and no systematic reviews. The RCT carried out by Boesen et al., (2019) evaluated the effect of adding corticosteroid to a HVUGI by comparing two groups. The two-arm study randomised subjects into a group who received a HVUGI containing corticosteroid and a group who received a HVUGI with no corticosteroid added. The other six studies employed a case series approach recruiting physically active patients who regularly took part in sport and already under the care of the researchers. All studies utilised the VISA-A questionnaire to measure pain and function pre and post intervention, which allowed comparisons to be made between groups.

The RCT conducted by Boesen et al (2019) consisted of a sample of 28 men of which 23 reported regularly taking part in sport. No explanation as to the decision to only include men in the study was provided, which challenges the generalisation of the results. Although an RCT should prevent selection bias pertaining to the allocation to the control and treatment arms of a study, this study failed to address bias in the recruitment process. Selection bias is considered a major flaw in a case series approach, the method adopted in all the other studies reviewed, with the studies recruiting patients who took part in sport or physical activity and at the time of the study under the care of the respective authors. The use of study samples consisting of physically active people would again limit the generalisation of the results to the general population. Two studies (Chan et al., 2008 and Gronbech Nielson et al., 2020) were retrospective studies, with some of the subjects being expected to recall pre- and post-intervention pain and function, up to two years after the application of the treatment intervention. Retrospective studies rely on information from a clinical and not a research database and as such some risk factors and information needed for the study may not have been recorded in the subjects' medical records. In addition, the time lag between intervention and data gathering can result in inaccurate recall of information (Talari and Goyal (2020). The other five studies reviewed were prospective studies. Although all seven of them showed some reduction in pain and improved function across the duration of the study period, the weaknesses

in the methodological approach adopted in the studies (case series) could question the significance of the results and their generalisation in practice.

All the seven studies used inclusion and exclusion criteria, which are considered important in optimising the internal and external validity of a study. Inclusion along with exclusion criteria help define the study population ensuring its homogeneity, reduce confounding and increase the likelihood of finding a true association between intervention and outcome (Salkind 2010). However, only one study (Boesen et al., 2019) demonstrated the use of a control group. The control group in the study who received a HVUGI without the addition of a corticosteroid could be considered an experimental or active control as the intervention would be considered an accepted treatment of non-insertional Achilles tendinopathy in its own right. The failure to use a control group in the other studies reviewed is considered a methodological weakness as any extraneous variables not eliminated by the inclusion and exclusion criteria can have a confounding effect on the results (Malay and Chung 2012). As all subjects in the studies had received previous conservative treatments the failure to use a control group and randomly assign subjects makes it difficult to ascertain the actual effect of the HVUGI on the reduction of symptoms reported. There is also a possibility that previous treatments administered could have had a delayed longer-term effect on clinical outcomes.

Additionally, the constituent components of the injectable solution used in all the studies questions the possibility of co-interventional bias due to concomitant therapies. Except for Wheeler (2014) and Boesen et al., (2019), the other five studies used a mixture of injectable saline and some other pharmacological agent which, in previous studies, have been shown to improve symptoms when used as a primary intervention. Chan et al (2008), Humphrey et al., (2009), Resteghina and Yeoh (2012) and Gronbech Nielson et al (2020) all added 25mg of hydrocortisone and local anaesthesia to the injectable saline. Studies have shown that the use of hydrocortisone reduces any localised inflammation in the area around the tendon and may well reduce symptoms if administered in isolation. This is highlighted in the RCT conducted by Boesen et al (2019) who reported statistically significant improvement in the VISA-A score, and tendon thickness when a corticosteroid was added to the HVUGI (treatment arm) when compared with HVUGI without the addition of corticosteroid (control arm). Maffulli et al., (2013) added 25 mg of aprotinin and local anaesthetic to the saline. Aprotinin inhibits the effect of collagenase, which has been found to be increased in Achilles tendinopathy and is thought to be responsible for the breakdown of collagen, a structural component of the tendon. In addition, Maffulli et al., (2013) administered a second injection containing 25mg of

hydrocortisone instead of aprotinin in subjects who continued to complain of pain at a two week follow up appointment, therefore confounding further the issue of concomitant therapies. All studies used a local anaesthetic agent to reduce any immediate post injection pain and discomfort and would not be expected to have any other treatment function or effect on the long-term pain relief. Bupivacaine hydrochloride would expect to provide anaesthesia for approximately eight hours post injection with lignocaine providing less than two hours of localised pain relief.

Besides variation in the pharmacological makeup of the injection, Chan et al., (2008), Resteghina and Yeoh (2012) and Beosen et al., (2019) also instigated a concurrent eccentric exercise plan and graded return to activity as part of their intervention. The literature shows that eccentric loading can reduce symptoms and improve function in patients with non-insertional Achilles tendinopathy (Mafi et al 2001). What cannot be determined from these studies is whether a HVUGI consisting of only injectable saline and local anaesthetic is more effective in reducing pain and improving function than an eccentric loading exercise plan. The failure in these studies to control confounding variables and the contraindications to the use of corticosteroids and sclerosing agents in tendinopathy has created a gap in the research literature about the effect of HVUGI (consisting of injectable saline and local anaesthetic only) and the reason to consider a future RCT and the requirement for this feasibility study.

The inclusion and exclusion criteria adopted in all studies where similar apart from Humphrey et al (2009) who failed to provide any details. Inclusion criteria focused on an athletic population who regularly took part in sport In addition, all subjects eligible for inclusion in the studies had all failed to respond to previous treatment consisting of a 12-week eccentric loading exercise programme. Maffulli et al., (2013) also included subjects who in conjunction to eccentric loading had received other conservative treatments including immobilisation, and the administration of a steroid injection, both of which could have contributed to long term improvements (Boesen et al., 2019). In the other studies those with previous surgery to the tendon were excluded, along with those who had had a previous partial or complete tear. Resteghini et al. (2013) also excluded those who had a previous steroid injection as repeated hydrocortisone injections can weaken the tendon making it more susceptible to rupture.

4.5.3 Summary of the review of HVUGI

In the studies which measured neovascularity and tendon thickness, the administration of a HVUGI appeared to cause a reduction in both. However, with regards to tendon thickness the

use of hydrocortisone has also been shown to reduce tendon thickness which was added to the injectable saline in all but one of the studies reviewed. This concurs with the results from the study by Boesen et al., (2019) which saw a reduction in tendon thickness with the application of a HVUGI consisting of injectable saline and local anaesthetic (control arm) and in a group who received a HVUGI consisting of injectable saline, local anaesthetic and corticosteroid (intervention arm). The reduction reported in both groups was greater in the intervention arm of the study which included corticosteroid. However, this greater reduction in tendon thickness appeared to be a short-term effect recorded at 6 and 12 weeks post injection but with no difference noted between the groups at 24 weeks. This raises the issue of cointervention bias as the reduction in tendon thickness reported might be a consequence of the hydrocortisone, or the high volume of saline or combination of both. A reduction in neovascularisation concurs with the theory that the high volume of saline introduced, mechanically breaks the neovascular bundles which occur in Achilles tendinopathy.

The review of the current literature pertaining to the use of HVUGI has identified some important issues which help shape the methodological approach adopted in this feasibility study. All the studies identified some improvement in symptoms with the administration of HVUGI and as such warrant's further investigation. However, as previously discussed only one study utilised a control group. Lack of a control group is considered a major methodological flaw of an interventional study. This is further compounded by the addition of other pharmacological agents to the injectable saline. These additional agents have been used in isolation in the treatment of Achilles tendinopathy and could therefore be considered concomitant therapies. Therefore, it is difficult to ascertain the actual effect of the high volume of injectable saline on the condition. Therefore, the study presented in this thesis uses an RCT study design sampling people from the general population reporting Achilles tendinopathy, treated either with an eccentric exercise loading programme (control group) or HVUGI (intervention group). In all the studies reviewed the volume of injectable saline was 40ml and all added a local anaesthetic to reduce the pain and discomfort associated with the injection of saline. Therefore, it would be considered appropriate in this study to do the same and inject 40ml of injectable saline along with a local anaesthetic. However, no other additives would be considered to reduce co-interventional bias.

4.6 Analytical review of the research literature pertaining Eccentric Loading Exercise Programmes for the treatment of Non Insertional Achilles tendinopathy.

A systematic search of the following databases was carried out using a text word search

- CINAHL
- Medline
- SPORTDiscuss
- Scopus
- Cochrane Database of systematic reviews

A systematic search of the literature was carried out between September 2014 and July 2020.

Several search terms where used which included the following, which are detailed in table 4.3.

Table 4.3 PICO template to identify and combine key words used in the electronic search of the literature for eccentric loading

Column treatment combined with OR	Population /Condition AND	Intervention AND	Comparative intervention AND	Outcome AND
OR	1.Achilles tendinopathy	7. eccentric loading	9.eccentric loading	11.VISA-A
OR	2.Non –insertional Achilles tendinopathy	8.exercise therapy	10. concentric loading	12.VAS
OR	3.Mid-portion Achilles tendinopathy			13.Tendon thickness
OR	4.Achilles tendinosis			14.Neovascularity
OR	5.Achilles tendonitis			
	6 Combine 1-5 using OR	11 Combine 7-8 using OR	17 Combine 9-10 using OR	22 Combine 11-14 using OR

The use of the PICO template in table 4.3 details the search terms used to describe the population, intervention, comparative intervention, and outcomes for the literature search

carried out for eccentric loading. In each column are key words used to describe each column heading. The key words in each column are combined by using OR. This finds citations containing any of the keywords. The columns are then combined using AND which finds citations that contain all the specified terms. This method was repeated for searching each database.

The search initially identified 8645 published items in peer reviewed journals, further filtering of the literature was carried out which reduced the number to 267. Several duplications were highlighted in the search and were subsequently removed. This left 94 published reports. These 94 reports could be divided into two distinct groups. The first group was studies where eccentric loading was the trial intervention whilst the second group consisted of studies where eccentric loading was used in a comparative trial as an experimental control group. This review concentrated primarily on studies which evaluated eccentric loading as a trial intervention and the papers reviewed are detailed in the table in appendix 8.

4.6.1 Physiological effects of eccentric loading

The review of the literature identified that the studies focused on the physiological effects of eccentric loading and concentrated primarily on two main aspects. Firstly, the structural changes to the tendon associated with the tendinopathy / injury and how these changes are affected by the eccentric loading exercise programmes and secondly the effect on perceived pain and function using a PROM.

Patients presenting with Achilles tendinopathy complain of pain usually around a thickened portion of the Achilles tendon which is also painful when palpated. Examination using Doppler ultrasound imaging shows disorganisation of the tendon fibres and the presence of neovascularity. Eccentric loading of the Achilles tendon is thought to help normalise the tendon by reducing the thickness, normalising tendon structure and reducing neovascularity. This was illustrated by Ohberg et al (2004) who showed that after 12 weeks of eccentric loading, the tendon thickness reduced and there was normalisation of the tendon structure. The study used a case series approach with no comparison made with a control group of subjects with Achilles tendinopathy who did not carry out eccentric loading exercises. The authors suggested that the use of a control group in their study would have been unethical in a population of subjects who had long standing Achilles tendon pain.The sample consisted of 34 patients with 45 painful Achilles tendons. All tendons were examined using colour Doppler ultrasound and exhibited neovascularity, disordered fibres and thickening of the tendon around its mid-portion. Four

subjects were lost to follow up resulting in the evaluation of 30 patients with 41 painful tendons. Thirty six of the 41 tendons were pain free on loading on completion of the eccentric loading exercise programme of which 34 exhibited a return to normal tendon structure. Thirty two of the 34 pain free tendons showed no evidence of neovascularity whilst 2 still exhibited some minor evidence. In the 5 tendons which had not improved, neovascularity was still evident. The authors reported that the physiological changes shown on ultrasound correlated with reduction in symptoms and satisfaction with treatment. The residual neovascularity was reported as the cause of the continued pain in the 5 tendons that did not improve. The mean follow up was 28 months ranging from 3 months-48 months. The long follow up time and the failure to use a control group challenges the results of this study as it fails to minimise the effect of all variables and as such the certainty that the results are due solely to the eccentric loading exercise programme.

Similarly, de Jonge et al., (2015) reported normalisation of the tendon structure following eccentric loading in 54 patients with non-insertional Achilles tendinopathy when compared to an aged matched asymptomatic control group (n=26). This study was part of a randomised trial using eccentric loading alongside either saline or platelet rich plasma injections. The study reported the normalisation of tendon structure was not significantly different to the structure exhibited by the asymptomatic control group at 24 weeks. However, the study failed to find an association with normalisation of tendon structure and reduction in symptoms.

This relationship between the reduction in pain and the normalisation of tendon structure (including the reduction in neovascularity), was considered in a systematic review by Drew et al., (2014) The study assessed the risk of bias using the Cochrane back review group risk of bias tool described by Furlan et al., (2009). The review included both RCTs and non RCT designed studies to reflect the evidence base as a whole. Therefore, in addition to assessing the risk of bias, a qualitative analysis of the included studies was also carried out by at least two researchers to classify studies as either high or low quality based on their methodological approach. Of the 18 studies reviewed 8 demonstrated a low risk of bias whilst the other 10 a high risk of bias.

The study reported strong evidence from 4 RCTs with a low risk of bias and one low quality study with a high risk of bias that a reduction of pain is not associated with a reduction in neovascularity, whilst 2 low quality studies with a high risk of bias supported the association. From a functional perspective there was strong evidence from 2 RCTs with a low risk of bias

and one low quality study with a high risk of bias to suggest an improvement in function was not associated with a reduction in neovascularity. However, moderate evidence from 1 RCT with a low risk of bias did suggest an improvement in function was associated with a reduction in neovascularity. When considering the evidence for the reduction in pain and its association with a reduction in structural abnormalities the evidence was conflicting. One RCT and 1 non RCT supported the association whilst 1 RCT and 1 non RCT showed no association.

Some important observations to note regarding the finding of this systematic review are the acknowledgment of the authors regarding the poor inter-rater reliability of both grey scale ultrasonography and MRI in observing structural changes in tendons. According to Zhang et al., (2018) grayscale ultrasound can diagnose significant thickening of the Achilles tendon but has poor sensitivity and specificity to early-stage thickening associated with non-insertional Achilles tendinopathy. However, compared with MRI, ultrasound provides improved views of the internal structure of the tendon. With regards to neovascularity, the findings were thought to be influenced by the lack of standardisation with examination with many utilising Ohberg's modified neovascularity score whilst others used less robust methods with poor validity and reliability.

The variations in sensitivity between power and colour Doppler was also noted by the authors. Colour Doppler converts blood flow measurements into an array of colours to help show the speed and direction of blood flow through a vessel whilst power Doppler uses the amplitude of Doppler signals to detect moving matter. A study by Richards et al., (2005) compared colour and power Doppler ultrasound in the examination of the microvascular response in Achilles' tendinopathy and reported that power Doppler shows more tendon microvascularity and the increased sensitivity to blood flow is better at quantifying the amount of neovascularity than colour Doppler ultrasound.

A study by Rees et al., (2008) used a combination of motional analysis, force plate data and real time ultrasound to measure the forces and changes in length of the Achilles tendon when performing eccentric and concentric loading exercises. The study found that there was no significant difference in the peak tendon force or tendon length changes when comparing eccentric and concentric exercises, however high frequency oscillations noted in the Achilles tendon during eccentric loading where like those seen in bone remodelling (Rees et al., 2008).

In addition, Slater et al., (2010) reported an increase in the Pressure Pain Threshold following eccentric loading exercises and hypothesised that the hypo- analgesic effect may aid in the management of Achilles tendinopathy.

Due to the lack of consensus pertaining to the physiological effects of eccentric loading of the Achilles tendon, this review highlights the importance of the added use of a PROM in studies evaluating the effect of eccentric loading as the patients' perception of pain and changes in functional status are key elements of any evaluation clinically.

4.6.2 The effect on pain and function associated with eccentric loading exercises

In the previous section the literature pertaining to the physiological effects were discussed. In this section the literature pertaining to the effect of eccentric loading exercises on pain and function will be reviewed.

It was the publication of the seminal work of Curwin and Stanish in 1984 which introduced eccentric loading as part of the rehabilitation process for those suffering with Achilles tendinopathy. Prior to that publication the mainstay of treatment had been rest, immobilisation, Non-Steroidal Anti Inflammatory (NSAID) drugs and corticosteroid injections. Although these measures did reduce the pain, the associated immobilisation did cause considerable muscle atrophy and this, along with the administration of corticosteroid injections, resulted in weakening of the tendon. The programme developed by Curwin and Standish in 1984, and used in their follow up study in 1986, involved a three-stage approach which consisted of stretching the tendon, followed by loading the tendon (tendon loaded through increase in load and by increasing speed of contraction) and a final post-exercise stretching similar to those performed pre-exercise. The eccentric loading exercises carried out consisted of three sets of 10 performed once daily for six weeks. The 1986 study employed a case series approach which included 200 consecutive patients referred with Achilles tendinopathy. The failure to use a control group is considered a methodological weakness as any extraneous variables not eliminated by inclusion and exclusion criteria can have a confounding effect on the results. In addition, no validated PROM was used with a good outcome recorded as relief of pain. The results showed that 44% of the patients experienced complete relief of pain and functional impairment whilst 43% reported a marked decrease in symptoms. Of the remaining patients 9% experienced no relief from the exercise plan whilst 2% saw a deterioration in their symptoms. It is surmised that the remaining 2% were lost to follow-up as no mention of them was made in the report.

Alfredson et al., (1998) modified the Curwin and Standish (1984) protocol by removing the concentric component from the exercise plan and piloted the plan on 15 recreational sports people. The study did employ a comparable group which received conventional treatment of rest, NSAIDs, changes in footwear and physical therapies. However, there was no reference to a randomisation process being employed, thus creating a possible sampling bias. The Alfredson et al (1998) protocol consisted of a 12-week programme of eccentric loading (heel drop exercises) exercises carried out twice daily. The eccentric loading exercises consisted of three sets of 15 exercises carried out with the knee straight and then followed by three sets of 15 exercises with the knee flexed. The protocol advised patients to expect some degree of pain and discomfort whilst performing the exercises. The study found that all patients in the eccentric loading exercise group returned to their pre-injury activity levels after 12 weeks, whilst those in the control group were all referred for surgery. In 2001 Silbernagel and colleagues developed another 12-week programme for the conservative treatment of non-insertional Achilles tendinopathy. This programme is referred to as the 'Silbernagel combined protocol' and incorporates a three-phase programme which consists of eccentric-concentric loading exercises, followed by eccentric loading then fast loading dynamic exercises. They hypothesised that this three-phase approach mimics the loading of the tendon during gait and other physical activities whereby the tendon is exposed to both types of contractions, eccentric contractions to absorb load and concentric contractions for propulsion. To evaluate this programme, they carried out a RCT comparing their programme with a concentric exercise programme. They used a Visual Analogue Scale (VAS) pain score as an outcome measure and found that this programme saw a greater reduction in the VAS score than the concentric exercise group when evaluated at 6 weeks, 3 months and 6 months. This reduction was also noted at a 1 year follow up. Of the patients in the trial group 60% reported a full recovery and return to activity compared with 25% in the concentric exercise group. Although the results are encouraging the programme is complex and difficult to follow. The use of dynamic exercises in a non-athletic population could prove challenging and have a negative effect on adherence.

Although all three protocols have shown merit it is the one developed by Alfredson et al., (1998) which is most referenced in the research literature and the one adopted in clinical practice. No explanation is provided in the literature as to why it is the protocol most used. Stasinopoulos and Manias (2012) carried out a pilot study to compare protocols developed by Alfredson et al (1998) and Curwin and Standish (1986). Subjects with non-insertional Achilles tendinopathy were assigned to two groups one following the Alfredson protocol and one the

protocol developed by Curwin and Standish. In both groups improvement in the VISA-A score was found but greater in the group that followed the Alfredson protocol. Combined with being a relatively simple protocol, this evidence illustrating higher VISA-A scores (higher scores are better) may indicate why the Alfredson protocol has become so popular.

The Alfredson protocol was used by Mafi et al., (2001) in a study which compared eccentric loading to concentric loading on a sample of 44 patients with severe Achilles tendinopathy. The patients had been referred for surgical consideration and had been symptomatic for a mean 21 months (range 3-120 months). The groups were evenly matched for numbers, mean age and gender. The authors did apply inclusion and exclusion criteria and carried out a randomisation process. The study used the VAS as an outcome measure and the results showed that 82% of patients in the eccentric exercise group were satisfied and returned to activity. In those patients who were satisfied, the VAS score reduced from 69 to 12 post-treatment, indicating a significant improvement. In the 18% that were not satisfied, the post-treatment VAS score was 44. This compares with the concentric exercise group where only 36% were satisfied and returned to activity. The VAS score reduced from 63 at baseline to 9 post intervention. The 64% that that were not satisfied had VAS score post intervention of 60. The results of this study concur with the results of the pilot study carried out by Alfredson et al., (1998) showing good clinical results for eccentric loading exercises. The study evaluated eccentric loading exercises in 15 recreational athletes with what they described at the time as Achilles tendinosis and compared it to 15 recreational athletes with the same diagnosis but treated conventionally which included rest, non-steroidal inflammatory drugs orthoses and an ordinary training programme. Although the study used a comparison group the subjects in the study were not randomised raising the possibility of selection bias. The small sample size of athletes also suggests weaknesses in the study design and the generalisation to the general population. However, irrespective of these weaknesses in the study design the Alfredson protocol continues to be used extensively in clinical practice as a non-surgical treatment.

Fahlstrom et al. (2003) compared the effect of eccentric loading on two groups of consecutive patients presenting with non- insertional and insertional Achilles tendinopathy. All the patients were physically active and were grouped based on the location of their Achilles tendon pain (insertional or non-insertional). The study found that 89% of those with non-insertional Achilles tendinopathy was satisfied and returned to pre-injury activity along with a subsequent reduction in the VAS score. However, eccentric loading was seen to be less effective in those with insertional Achilles tendinopathy with only 32% of patients in the group satisfied and able

to return to pre activity levels. Similarly, the VAS score post intervention was similar to that reported by Mafi et al., (2001).

Sayana and Maffulli (2006) evaluated the effect of a 12-week eccentric loading programme described by Alfredson (1998) on sedentary individuals. This was a departure from earlier studies which tended to focus on athletic populations. The sample included 34 patients, 18 men and 16 women with a mean age of 44 years (range 23-67 years) for the men and a mean age of 51years for the women (range 20-76). This study utilised the VISA-A questionnaire to measure pain and function. The case series approach adopted in this study raises the issue of selection bias and is considered a methodological weakness. The patients in the study were monitored in outpatients every two weeks, whilst also receiving a telephone call each week. Although this continued monitoring improves compliance pragmatically this level of monitoring would not be possible in clinical practice and therefore one might question the applicability of the finding to the general population. The study showed that 44% (15) did not improve with eccentric loading and proceeded to receive peritendinous injections of aprotinin. These results suggest that eccentric loading exercises may not be as effective in the sedentary population as they maybe in those who are physically active.

However, Maffulli et al (2008) in a follow up study on athletic patients with unilateral non insertional Achilles tendinopathy, found a 12-week eccentric loading exercise programme resulted in better results than previously found in a sedentary population. (Sayana and Maffulli 2006). Of 45 patients 27 (60%) reported an improvement in their symptoms. Of the 18 who failed to improve following the ELE programme, 5 improved with a peritendinous injections of aprotinin. The 10 who had failed to respond to eccentric loading and the follow up injection proceeded to surgery, whilst 3 patients refused any further treatment. Again, the authors demonstrated a adopted a case series approach which raises the issue of possible of selection and co-interventional bias.

The research publications reviewed all reported that eccentric loading exercises improved symptoms in patients with non-insertional Achilles tendinopathy irrespective of the PROM used. Although the early studies failed to use a validated outcome measure, the introduction of the VAS and then more recently the VISA-A questionnaire, has made comparison between studies easier. There were methodological weaknesses noted in some of the studies which included the case series approach, with a lack of a control group and as such failure to carry out any form of randomisation. However, the reported improvement seen with eccentric

loading and the relative ease in which it can be delivered with low costs and minimal harm have provided the justification for considering it as an initial intervention for the treatment of non-insertional Achilles tendinopathy and as such provides the mainstay of conservative treatment. As a result, it is common to see eccentric loading exercises used as an experimental control (including this study).

4.7 Implications for study design.

This chapter has reviewed the literature pertaining to the epidemiology of non-insertional Achilles tendinopathy as well as a critical review of the research literature pertaining primarily to the use of HVUGI and eccentric loading exercise for its management. Such evidence is presented as it is key to justifying the need for the RCT trialled in this thesis.

The studies reviewed in the critical analysis of HVUGI in the treatment of Achilles tendinopathy all used a quasi-experimental design. This approach although like a trial or experiment has one major fundamental difference in that subjects are not randomly assigned into treatment groups. This is considered a significant methodological flaw which was observed and reported in the critical review. The failure to use a control group makes it difficult to ascertain with any confidence that the results were because of the high volume of saline injected under ultrasound guidance or some other confounding effect. Some possible confounding effects included the addition of pharmaceutical agents to the saline which have previously been reported to have a treatment effect when used in isolation. In addition, the use of different post injection exercise regimes may have also had a confounding effect. There was also some evidence of selection bias in all the studies, which is considered another weakness in this type of research design. All the studies reviewed involved athletically active subjects which may not be truly representative of those in the general population who suffer with non-insertional Achilles tendinopathy.

Therefore, the aim of this study was to investigate the effectiveness of HVUGI in the treatment of non-insertional Achilles tendinopathy employing a methodological approach which would reduce or eliminate the possible confounding effects that the previous studies have failed to do. Creswell (2014) described experimental research as a method to determine if a specific treatment influences an outcome. Therefore, an experimental design is utilised in this study. The usual approach in experimental design is to randomly assign participants to either an intervention or control group. Although it is common for the control group to receive no treatment intervention, one would have to consider the efficacy of a study which would assign

participants with a painful condition such as non-insertional Achilles tendinopathy to a group which would receive no intervention /treatment. Therefore, to utilise a true experimental design in the proposed study could be considered unethical and would have influenced recruitment and retention during the study. As a result, it was considered appropriate to provide participants in the control group with some form of treatment intervention. This was addressed using a comparative experimental design. In this study the control group received the current accepted non-surgical intervention of eccentric loading exercises.

The research methods literature discusses the concept of independent and dependant variables when considering experimental design. The independent variable refers to the intervention, which is carefully controlled by the researcher, whilst the dependent variable refers to what is measured in the experiment. In comparative experimental studies both groups would receive a treatment intervention. Therefore, in this study the independent variables or treatment intervention was the administration of the HVUGI (injectable saline + local anaesthesia) to one group and the initiation of an eccentric loading programme (generally accepted current approach) in the comparative control group.

The dependant variable widely used in the literature pertaining to the treatment of Achilles tendinopathy is the VISA-A questionnaire. This has been found to be a valid and reliable tool in evaluating pain and function in Achilles tendinopathy. This would be considered the primary outcome measure and would allow comparisons to be drawn with other studies evaluating the effectiveness of treatments for Achilles tendinopathy. Secondary outcome measures could be the measurement of neovascularity and Achilles tendon thickness both of which are reported to be reduced by the administration of a HVUGI. The objective measure of Neovascularity uses the modified Öhberg scale, a measurement tool which has been shown to be a reliable and valid tool with good inter and intra tester reliability. The measurement of tendon thickness is performed using Doppler ultrasound. To reduce any inter-tester variability when measuring the thickness of the tendon, all measurements would be carried out by a single radiographer /radiologist, whilst intra-tester reliability could be evaluated prior to the commencement of the study.

Bowling (2014) suggested that pre and post testing was necessary to measure the experimental effect of the intervention in an experimental group. In the proposed study pre (baseline) and post testing would be carried out in all groups to allow the analysis of the experimental effect. The critical review of the literature carried out identified variations in the post-testing period

from 3 weeks to 1 year. As the research evidence suggests that eccentric loading exercises should be carried out for 12 weeks, then the first post-test evaluation of all the groups should be at a period no earlier than 12 weeks to ensure comparisons can be drawn between the independent variables or interventions. To establish if any long-term effects are provided by the interventions, further follow-up testing could be carried out at 6 and 12 months. However, evaluating over this longer period might result in attrition particularly if participants have any reoccurrence of symptoms. In addition, with the restrictions of time and the fact that this is a feasibility study, then follow-up was limited to 12 weeks.

A cornerstone of experimental research design is the use of randomisation, allocating participants to either a control or intervention group. The aim of random sampling is to ensure that all participants in a study have an equal chance of selection into either the intervention or control group (Polgar and Thomas 2013). Although most research studies define inclusion and exclusion criteria there are often numerous diverse characteristics within a sample which cannot be considered by the study. These factors can result in random errors which can be obscure and are often difficult to eliminate (Hicks 2004). Random allocation is considered important in controlling these variations in subjects which can have a confounding effect on the results. Bowling (2014) suggested that the random assignment of participants reduced the risk of results being affected by extraneous variables, not by elimination but through even distribution across the groups.

In addition to random allocation, sample size is also a principal issue to consider in the planning of an experimental study. It is hoped that by carrying out this feasibility study a power calculation will be possible to help provide an estimate of the sample size to be used in any future RCT. When considering sample size, it would seem logical to assume that the bigger the sample size the better. However, studies are often governed by both time and economic costs, and it is therefore important that the sample size is calculated to ensure it is of sufficient size to make inferences from the sample to the population. It is also important that the sample is representative of the population (Polgar and Thomas 2013). Hicks (2004) also identified that the greater the sample size the more chance that small effects of the intervention could be statistically significant, whilst showing little clinical significance. Hicks (2004) reported that the sample size depends on the effect size of the intervention, and the power of the test to detect the size of the effect. Determining the size, composition, and randomisation of the sample will be an important consideration when developing the research design.

Prior to carrying out an RCT it is considered good practice to carry out a feasibility study to ensure that the methodological approach including the randomisation processes work and that there are no adverse reactions to the intervention. It also helps to establish the rates of eligibility, recruitment and retention, and allows the calculation of the sample size which are essential considerations when planning a larger study. It is imperative that when embarking on a large-scale study that the research team are confident that they will be able to recruit sufficient subjects within a realistic timeframe and that retention is maintained throughout the study. Only by carrying out a feasibility study can we ensure that the building blocks for a larger study are in place and that we can proceed with confidence. It also instils confidence in potential funders if a research team can provide evidence from a feasibility study. Therefore it was anticipated that the aims and objectives of this feasibility study detailed in section 4.8, would identify any weaknesses in the study design which could be considered in any future trial.

4.8 Aims and objectives

4.8.1 Study aims

The aim of this study was to assess the feasibility of conducting a future definitive randomised control trial to compare HVUGI with eccentric loading exercises in reducing pain and improving function in subjects with non-insertional Achilles tendinopathy

4.8.2 Primary objectives

The primary objectives detailed below were developed to assess the feasibility of study processes including rates of participant recruitment, retention, and safety.

- To calculate the eligibility rate- the number of eligible subjects as a proportion of the total screened patients in a three-month period.
- To calculate the recruitment rate- the number of recruited patients as a proportion of the number of eligible patients within the three-month period.
- The test the proposed method of randomisation to achieve an even balance of subject numbers in each arm of the study.
- To evaluate adherence with the intervention- the eccentric loading group are required to carry our relatively painful exercises for 12 weeks- adherence was evaluated with the use of an adherence diary which was completed by the subject and recorded frequency (number of sessions per week) and intensity (number of repetitions per session).

- To evaluate follow up rates- the total number of recruited subjects who are followed to the end of the study period.
- Evaluate the outcome measures utilised in the study- VISA-A questionnaire / Ohbergs modified neovascularity score.
- Record any adverse reactions to the HVUGI or the eccentric loading programme.

4.8.3 Secondary objectives

The secondary objectives were developed to explore trends in treatment effect

- Describe the effect of high-volume ultrasound guided injections compared with eccentric loading on pain and function in subjects with non-insertional Achilles tendinopathy.
- Describe the effect of high-volume ultrasound guided injection compared with eccentric loading on tendon thickness in subjects with non-insertional Achilles tendinopathy.
- Describe the effect of high-volume ultrasound guided injections compared with eccentric loading on neovascularity in subjects with non-insertional Achilles tendinopathy.

No hypothesis testing was carried out as part of this pilot/ feasibility study as recruitment rates were part of the primary outcomes measures and will determine the necessary sample size needed to carry out a larger scale study suitable powered to 0.8 with a level of significance of ≤0.05.

CHAPTER 5 MAIN EXPERIMENTAL PHASE

5.1 Introduction to the chapter

This chapter focuses on the main experimental phase of the thesis and applies a developed protocol which included the ethical approval process, screening recruitment, and randomisation of participants. It will also provide a detailed description of how the High-Volume Ultrasound Guided Injection (HVUGI) was administered in those randomised to the treatment group and the advice and guidance given to those in the control group who performed an eccentric Loading Exercises programme. The process of ultrasound scanning, and the application of the Patient Reported Outcome Measures (PROM) will also be discussed.

5.2 Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki ethical principles (2013). Prior to the commencement of recruitment and data collection, ethical approval was sought and granted initially from the NHS, Invasive or Clinical Research Ethics Panel at the University of Stirling. As this study was conducted as partial fulfilment of the professional doctorate programme, university ethics were required before seeking external approval. Once university ethics had been granted an application was made to NHS Southeast of Scotland Research Ethics Committee (IRAS online application) and approval subsequently granted (REC no 17/55/0107). Once ethical approval was granted, approval for the study was sought from the local Research and Development unit of NHS Lothian (R&D No 2018/0079

5.3 Recruitment of participants

Participants (n=33) were recruited from patients referred to the foot and ankle service at a large teaching hospital in Scotland, United Kingdom. Referrals were from General Practitioners (n=25) and other health care professionals including podiatrists (n=5) and physiotherapists (n=3).

All referrals to the foot and ankle service were triaged by the Consultant Podiatrist, who determined whether the patient was seen by a specialist podiatrist or consultant orthopaedic surgeon. The decision on the appropriate referral pathway was determined by the information provided by the referrer. Those patients suspected of having non-insertional Achilles tendinopathy by the consultant podiatrist were triaged to a specialist podiatrist in the direct care team. All patients referred in a six-month period with the clinical signs and symptoms of noninsertional Achilles tendinopathy (pain, impaired function and swelling in and around the Achilles tendon) were advised of the study (n=63). Of the 63 patients screened, 20 were excluded as result of having pain and symptoms in both Achilles tendons, had undergone previous treatment or their symptoms were suggestive of insertion Achilles tendinopathy. The remaining 43 eligible to enrol in the study were provided with a Patient Information Sheet (Appendix 1). Following careful consideration of the information provided and the opportunity to discuss the study with the PI, 10 declined to participate. The 10 patients not interested in participating were treated in accordance with the local care pathway which recommends that all patients with Achilles tendinopathy are prescribed an eccentric loading exercise programme like that used as the control intervention in this study. The recruitment of participants is

summarised in figure 5.1. Baseline measures on figure 5.1 refer to the administration of the VISA-A questionnaire and the measurement of neovascularity and tendon thickness.

Patient referred to department of orthopaedics and trauma

Triaged by consultant podiatrist- numbers with non- insertional Achilles tendinopathy recorded for recruitment purposes

Patient given appointment with member of the direct care team in accordance with all new patients accessing service

Care team examines patient – initial diagnosis of non- insertional Achilles tendinopathy - Given PIS and patient consents to PI contacting them at least 24 hours after this initial contact (n=43)

If they agree to participate then patient were given an appointment for department of radiology (n=33)

On attending department of radiology - patients consented to take part in the study

Subject who did not consent or did not fulfil the inclusion criteria were referred for treated in accordance with current departmental practice

Once consented patient were randomised into group A or Group B

Control Group- (n=19) Scanned and baseline measures recorded- instigate eccentric loading exercises programme

In the event of abnormal scan patients withdrawn form study and referred for treatment n=2 (1 from group A and 1 from group B

Treatment Group (n=14) Baseline measures recorded HVUGI administered

Outcome measure at 3 months (n=13)

Outcome measure at 3 months (n=10)

Exit study

Exit study

Figure 5.1 Participant study pathway For those patients who did show an interest, consent was sought to allow the PI to contact them at least 24 hours after this initial consultation. If

following a telephone consultation with the PI the patient agreed to participate, they were given an appointment to attend the Department of Radiology at the hospital. The telephone consultation ensured the prospective participant had an opportunity to discuss or seek clarification on any aspect of the study, as well as enabling the PI to identify inclusion and exclusion criteria which may determine the participant's suitability. Those who chose not to participate (n=10) due to being unable to attend on the dates offered or the uncertainty of treatment they might receive were given a further appointment to initiate appropriate treatment.

On attending the Department of Radiology, participants were given a further opportunity to discuss the study and if at that stage they were happy to participate then they were asked to give written consent (Appendix 2). Patients who did not consent (n=0) or did not fulfil the inclusion criteria (n=2) were excluded from the study and treated appropriately based on the clinical findings and their past medical history.

The hard copy of the consent forms and contact details of the participants were the only nonanonymised data in the study and were stored in a locked filing cabinet in the PI's office. On completion of the study (submission of the thesis) the non-anonymised data will be destroyed.

5.3.1 Inclusion and Exclusion criteria

All prospective participants were assessed against a series of inclusion and exclusion criteria. The inclusion criteria define the key features of the target population which will be used to answer the research question. On the contrary the exclusion criteria are features of potential study participants who meet the inclusion criteria but might present with additional characteristics that could confound the results of the study. The inclusion criteria are unique to each study and are based on knowledge of the condition under investigation. In table 5.1 the inclusion and exclusion criteria used in this study:

Table 5.1 inclusion and exclusion criteria applied to prospective participants.

INCLUSION CRITERIA	EXCLUSION CRITERIA
Aged 18 or over	Concurrent musculoskeletal problem- such as ankle sprains or osteoarthritic changes in the ankle
Capacity to give informed consent	Has a diagnosed rheumatological disorder such as Rheumatoid disease
Clinical diagnosis for unilateral noninsertional Achilles tendinopathy* / plus diagnostic ultrasound confirmation	Suffered total or partial tear of the Achilles tendon
English Language as a first language	Previous injection for non-insertional Achilles tendon
	Previous surgery to the Achilles tendon
	Patients with bilateral non insertional Achilles tendinopathy.
	Currently taking quinolone antibiotics (or in the prior 3 months)
	Previous allergy to local anaesthesia
	English is not the first language#

Clinical diagnosis criteria would include the following:

- *Pain and tenderness on palpation of the Achilles tendon 2-6cm from the insertion into the calcaneus.*
    - *Evidence of tendon thickening on palpation of the Achilles tendon.*
    - *Negative Simmonds-Thompson test (Test to exclude tendon rupture)*

 # English not first language

Prospective participants where English was not their first language and would normally require translation services when assessing healthcare services were excluded. This was a result of no funding to employ the relevant translation services but would be necessary as part of a fullscale trial to ensure inclusivity. The VISA-A questionnaire has not been validated for all languages so again this poses some limitation on some eligible participant's dependant on their nationality being able to take part in the study.

Once consent had been given, participants were randomised as described in section 5.3 into either the control group (eccentric loading exercise programme) or treatment group (HVUGI). The PI administered the baseline VISA-A questionnaire to all participants in both groups (section 5.7.1). The consultant radiologist then carried out baseline measurements of tendon thickness and Ohberg neovascularity score (section 5.7.2) and administered the HVUGI for those randomised to the treatment group (section 5.9). The PI initiated the eccentric loading programme for those randomised to the control group after the baseline measures were carried out by the consultant radiologist. All ultrasound scan results were reported by the consultant radiologist in accordance with health board policy and recorded on TRAK (Electronic Patient records system). The referring GP was advised in writing that their patient had consented to participate in the study (appendix 3). Those patients choosing not to participate at this stage were assessed and treated as any routine new patient. At no stage in the process were these patients expected to wait any longer for their treatment than other patients accessing the service. At the time of data collection, the waiting times for an orthopaedic review appointment was 4 weeks.

5.4 Randomisation Process

The study randomly assigned participants into two groups. One group received the HVUGI (treatment group) whilst the other received the current standard intervention of an eccentric loading programme (control group). Randomisation was performed using the Sealed Envelope online randomisation programme (Sealed Envelope, London, UK). All eligible participants were given a unique 9-digit code which consisted of their date of birth plus a further three digits. The participant's unique identification code and names were stored separately on a password protected server which only the PI had access. The aim of storing them separately was to ensure anonymity of data collected. The participants were randomly allocated into the two groups using simple block randomisation block design (Lim and In 2019). The block sizes were four, six, and eight. The use of different block sizes removed the ability of the researchers to be able to work out sequencing whilst trying to ensure equivalent group size (Schulz and Grimes 2002). The randomisation system was accessed via a secure connection over the internet. This connection encrypted data between the PI's internet browser and the server. To achieve online randomisation the PI was required to provide the participant's unique identification code, the PI's email address and the randomisation system password set when registering the study with Sealed Envelope. On receipt of this information, the system

randomised the participant to treatment or control and notified the PI by email. For transparency participants were able to observe the PI log in their details and see a copy of the returned email detailing which group they had been randomised to.

5.5 Blinding.

Blinding was considered when designing the research protocol. Ideally, the PI would have been able to double-blind the study in order to reduce experimenter bias and possible placebo effect. Blinding of the participants was considered difficult due to the nature of the interventions, with one group receiving an injection and the others an exercise protocol. Consideration was given to blinding the clinician who measures the tendon thickness and neovascularity score. However, it was not possible to recruit a second consultant radiologist to be involved in the study and as such, the feasibility study was not blinded, but would be considered and costed in any future RCT.

5.6 Sample size

The aim of this feasibility study was to collect data on outcomes that may be used to inform a future large-scale trial and not prove the superiority of HVUGI over an ELE programme. Although one of the primary aims of this study was to assess the recruitment rates of participants into the study, it is still deemed good practice to set a sample size when designing a feasibility study. The method utilised to calculate the sample size in a main study cannot be used for a feasibility study and therefore several authors have suggested that a sample size be based on "a rule of thumb sample size estimate". These vary considerably from 24 (Julious 2005) to 70 suggested by Teare et al., (2014)., with other authors such as Kieser and Wassmer recommending 20-40 and Browne (1995) a sample of 30.

Julious et al., (2005) based their suggested sample size of 24 for a feasibility study, on several factors. A sample size of 24 is divisible by 2, 3, 4 and 6 and as such facilitates the use of various block sizes for randomisation. In addition, they also reported on the precision of the mean and variance used in estimating the sample size in a main trial. They illustrated that the precision for each increase in the sample size was pronounced up to 12 but less for increases in sample size beyond that number. Whitehead et al., (2015) described a method using the standardised effect size for the main trial if known. It was acknowledged by the authors that the effect size of the main trial is not always known and therefore provided approximate rules. They report that for a main trial designed with 80% power and a level of significance of ≤ 0.05 then a

medium effect size of between 0.3 and 0.7 would require a sample size of 20 and for a small effect size of between 0.1 and 0.3 that would be increased to 40. The plan in this study was to recruit 30 participants over a four-month period (extended to 6 months see section 7.3.2) was considered an appropriate size based on the literature and provide some indication of recruitment rates for possible future RCT.

5.7 Study Interventions

5.7.1 VISA- A Questionnaire - Measuring Pain and Function

The primary outcome measure used in this study was the Victoria Institute of Sports Assessment–Achilles (VISA–A) questionnaire. This questionnaire was administered to all participants who consented to take part in the study. It is a self-administered questionnaire which the participants were given time to complete. The PI was in attendance whilst the participants completed the questionnaire. It was completed after the randomisation process but prior to ultrasound scanning of the Achilles tendon which provided a baseline measure of pain and function associated with the participant's non-insertional Achilles tendinopathy. The VISA-A questionnaire was administered again at 12 weeks to both groups, which corresponded with completion of the eccentric loading exercise programme.

The VISA-A questionnaire is an inverted numerical rating scale and results in a score of 0-100, where an asymptomatic subject would score 100 (Iversen et al 2012). It consists of eight questions which cover three areas of pain, function, and activity, and is self-administered. It is a valid and reliable tool and since its introduction in 2001 has been adopted both in the UK and internationally to evaluate pain and function associated with Achilles tendinopathy (see section 4.3.1)

5.7.2 Ultrasound scanning to measure the Achilles tendon thickness and neovascularity

An ultrasound scan was performed, before and after the intervention, to measure the tendon thickness (millimetres) and neovascularity (Ohberg score). It was also used at baseline to identify any abnormalities in the tendon which might exclude the participation in the study. The ultrasound scan was carried out by a consultant radiologist who was a Fellow of the Royal College of Radiologists (FRCR) with 15 years-experience in musculoskeletal diagnostic and interventional ultrasound (one radiologist performed all measurements) using a Logiq E9 (GE Healthcare) ultrasound machine with a GE 9L-D probe. The participant was positioned for the

scan in the prone position with their foot freely hanging over the end of the plinth in a neutral position.

The ultrasound scan was reported in accordance with Radiology Department protocols and recorded on TRAK (Patient electronic records system). This ensured that the intervention and scan reports were available to ensure continuity of care for any future consultations that might take place out with the study.

Measuring tendon thickness

The Achilles tendon was scanned in both the transverse and longitudinal axis and a measurement taken of the anteroposterior dimension of the Achilles tendon at the thickened portion. Using the ultrasound machines integrated measurement device the tendon thickness measured in millimetres was recorded on the subject's data sheet using their unique identification code (Figure 5.2).

Figure 5.2 Transverse image of the Achilles tendon demonstrating a significant anterior to posterior thickening. The two crosses and joining line represent the measurement calliper and a recorded thickness of 13mm.
Measuring neovascularity.

Power Doppler ultrasound was used to identify and measure neovascularity. It was measured using the Modified Ohberg Neovascularisation Score (Table 5.2).

Table 5.2 Modified Ohberg score for neovascularity (adapted from Ohberg et al. 2001)

Ohberg's neovascularity Score	Description of neovascularity
0	No vessels visible
1+	One vessel visible mostly anterior to the tendon
2+	One or two vessels visible throughout the tendon
3+	Three vessels throughout the tendon
4+	More than three vessels throughout the tendon

This is a semi quantitative grading system, which has been shown to have excellent inter-rater reliability with an Interclass Correlation Coefficient (ICC) of 0.85 (Sengkerij et al., 2009). The measurement was carried out with the subject in the prone position with the feet positioned at the end of the treatment couch with the ankle in a neutral position. Care was taken to minimise the pressure of the probe on the skin to prevent obliteration of the vessels whilst carrying out the examination. The examination was carried out in the longitudinal and transverse planes with an example of transverse view of the Achilles tendon illustrated in figure 5.3

Figure 5.3 Transverse image of an Achilles tendon demonstrating neovascularity (red areas on scan) originating from the anterior region of the Achilles tendon. The modified Ohberg score for this tendon was +1.

5.8 Group A (Control Group) – eccentric loading exercise programme

On completion of the ultrasound scan carried out by the consultant radiologist the participants were given an eccentric loading programme by the PI. This included both written and verbal instruction. The information included a demonstration of the exercises along with details on the number of the daily sets and repetitions of each that required to be performed. The verbal information provided was echoed by written information (see appendix 4). Participants were also provided with a diary to record their adherence with the programme by recording the number of sets and repetitions carried out each day for the 12-week duration (Appendix 5).

The programme consists of a heel drop exercise carried out from the starting position illustrated in figure 5.4A firstly with the knee fully extended (Figure 5.4B) to eccentrically load the gastrocnemius and then with the knee flexed (Figure 5.4C) to eccentrically load the soleus. The programme is based on the Alfredsen protocol as first described in 1998 and requires three sets of 15 repetitions of each exercise, carried out twice daily in the morning and evening for 12 weeks. The participants were advised that they should expect to experience some pain whilst performing the exercises.

Figure 5.4 Eccentric loading exercises (Childress and Beutler 2013)

Following the completion of the 12-week exercise programme the participants were invited for a follow-up review in the department of radiology. The VISA-A questionnaire and an ultrasound scan were again carried out to measure tendon thickness and neovascularity. The measurements were reported on TRAK and on the subject's data sheet. The VISA-A score was also recorded.

If at this stage the participants were able to return to their pre-injury levels of activity because of improved levels of function and reduced pain reduced pain, then they were discharged back to their GP. At this point they were advised that within the following 6 months if they experienced any re-occurrence of symptoms, they could contact the department of orthopaedics and trauma for a follow up appointment without a referral from their GP. If at the 12-week review participants continued to experience pain and had limitations in function which affected their activities of daily living, then they were provided with a follow-up appointment in the department of orthopaedics for continued ongoing care.

5.9 Group B (Treatment group) - HVUGI

For those participants randomised to this group an initial ultrasound scan was carried out by the consultant radiologist to measure tendon thickness and neovascularity, with this process matching that described above in section 5.6.2. Following the initial ultrasound scan the participants were asked to remain in the prone position with the knee extended and the ankle in a neutral position. Prior to the administration of the injectable saline, and following

cleansing the skin with an alcohol swab, 10ml of 1% lidocaine (local anaesthetic) was administered anterior to the Achilles tendon. The aim of the local anaesthetic was to provide an anaesthetic block and therefore reduce pain during the immediate post-intervention period. Then, under ultrasound guidance and using aseptic techniques, a 21-gauge needle attached to a 30cm connecting tube was positioned between the anterior aspect of the Achilles tendon and Kager's fat pad. Under continued ultrasound guidance 40ml of injectable saline was administered targeting the area of neovascularity. On removal of the needle a sterile dressing was applied. This was carried out by the same radiologist who carried out the tendon measurements. On completion of the injection the participants were advised that the area around the Achilles would appear very swollen for about 24-48 hours. They were allowed to fully weight-bear immediately after the injection with only light activities recommended for 72 hours. After that, participants were encouraged to gradually return to activity.

A review was carried out at 12 weeks where patients were invited back to the clinic where the VISA–A questionnaire was administered again, and the score recorded on the subject data sheet. A follow-up scan measuring the tendon thickness and neovascularity was again performed by the same consultant radiologist who carried out the baseline scans and intervention. The ultrasound scan measurements were reported and recorded on TRAK as well as on the subject data sheet.

As with those subjects in the control group, if at 12 weeks the participants were able to return to their pre-injury levels of activity because of improved levels of function and reduced pain then they were discharged back to their GP. They were advised that within the following 6 months if they experienced any re-occurrence of symptoms, they could contact the department of orthopaedics and trauma for a follow up appointment without a referral from their GP. If at the 12-week review point participants continued to experience pain and had limitations in function which affected their activities of daily living, then they were provided with a followup appointment in the department of orthopaedics for continued ongoing care.

CHAPTER 6 RESULTS SECTIONS

6.1 Introduction to the chapter

This chapter will provide the statistical analysis for the data collected in relation to the primary and secondary aims of the study. The data from the study has been analysed using SPSS version

23. The primary aims were analysed using basic descriptive statistics with a focus on evaluating the feasibility of carrying out a large-scale RCT. The secondary aims were focused on the experimental data collected from the two arms of the study. It was acknowledged that hypothesis testing would not be carried out as part of this feasibility study, but the analysis of data might provide some information, which might be helpful for future planning (e.g. sample size calculations). The reason hypothesis testing was not considered was the sample size selected, although sufficient for a feasibility study was anticipated to be underpowered to provide any meaningful results regards the significance of the outcomes. However, the data was analysed in the normal manner, firstly checking the data for normality to help guide the appropriateness of the statistical analysis performed.

6.2 Demographic characteristics of the sample group

Thirty-three subjects volunteered to take part in the study. Two participants were withdrawn due to abnormal scans with one other voluntarily withdrawing. Of the 33 original participants, there were 20 males and 13 females with a mean age of 53.70 years $\pm$ 11.40 years.

6.3 Analysis of the primary aims

The Consolidated Standards of Reporting Trials (CONSORT 2010) provides guidance on the reporting of trials and by doing so aims to improve transparency in these studies. These guidelines were extended in 2016 to include pilot and feasibility trials conducted in advance of a future RCT and were consulted throughout this study to ensure the accuracy of reporting and to improve transparency of the results in informing a future RCT. The flowchart of recruitment illustrated in Figure 6.1 provides an overview of the recruitment and retention in this study and reported data is discussed in detail throughout this chapter. In order to improve transparency as suggested in CONSORT 2010 a draft manuscript for submission to the Pilot and Feasibility Studies Journal has been prepared (appendix 10)

6.3.1 Eligibility rate

The eligibility rate is the number of eligible subjects as a proportion of the total screened patients over a specified time period. In this study the data collection period was originally designed to be four months (based on the recruitment of 2 subjects per week) but was extended to six months due to reduced availability of the consultant radiologist during the trial period.

In the six-month period 63 patients were referred to the department of orthopaedics with the primary reason being Achilles tendon pain. Of those 68% (n=43) fulfilled the inclusion criteria (table 5.1) and were therefore eligible for the study.

There were several reasons why the 32% (n=20) were not eligible to take part in the study based on the exclusion criteria (see Section 5.3.1) and are illustrated in table 5.1. Of the 20 patients who presented with Achilles tendon pain eight had received previous treatment, seven had bilateral presentation and five had insertional Achilles tendinopathy.

Table 6 1- Non-eligibility criteria and number of patients identified in each category

Reasons for non-eligibility to participate in the study	Number of subjects (n=20)
Undergone previous treatment	8
Bilateral presentation of Achilles tendon pain	7
Insertional Achilles tendinopathy	5

6.3.2 Recruitment rate

The recruitment rate is defined as the number of recruited patients as a proportion of the number of eligible patients within the recruitment period (six months). Of the 43 patients who were eligible to take part in the study 33 (77%) were recruited. The 10 (23%) eligible participants who did not agree to take part cited time constraints and the uncertainty of the treatment to be provided as a result of the randomisation process as reasons for not participating.

6.3.3 Randomisation

The study used an online randomisation programme (Sealed Envelope London UK) and utilised a simple four, six and eight blocks design. The programme allowed for the randomisation of

up to 50 participants. Of the 33 participants randomised in the study, 19 were randomised to the Control group (ELE programme) and 14 to the Treatment group (HVUGI).

It was anticipated that if the sample size of the study had been 50 rather than 33 then based on the programme sequencing of the block sizes used then there would have been equal numbers in each group. Although Schulz and Grimes (2002) suggest that block randomisation can result in equal numbers in all arms of an RCT, it does detract from the unpredictability that can occur with simple randomisation. Though accepting the desire to have equal numbers in each arm of a study they considered that the unpredictability of randomisation can reduce selection bias resulting in unequal group sample sizes which they consider acceptable variance in studies.

6.3.4 Follow-up / retention rates

The follow-up rates are the total number of recruited subjects who are followed to the end of the study period.

Of the 33 subjects recruited into the study, two were excluded following abnormal ultrasound scans and referred on for appropriate treatment. Of the 31 subjects who were randomised into the control/treatment groups, eight were lost to follow up. One subject voluntarily withdrew as they were randomised to the control group and did not want to participate in the exercise programme. The seven other subjects who were lost to follow-up either failed to respond to follow-up appointment requests or were unable to make the review appointment on the allocated day or time. Of those seven subjects four were lost to follow-up in the control group which equated to a retention rate of 71% in that group and three in the treatment group which again equated to a retention rate of 77%. Overall, 74% (n=23) follow-up / retention rate was achieved in this study.

Screened

Screened prior to eligibility assessment

Excluded
(n=20)
Undergone Previous t/t
(n=8)

Enrollment

Assessed for eligibility
(n=43)

Excluded   (n=10)
Declined to participate (n=10)

Randomised

Allocation

Allocated to control group   (n=19)
Received ELE programme   (n=17)
Did not receive allocated intervention
Abnormal scan   (n= 1)
Voluntary withdrawal   (n= 1)

Allocated to treatment group   (n=14)
Received HVUGI   (n=13)
Did not receive allocated intervention
Abnormal scan   (n=1)

Follow-Up

Lost to follow-up   (n=4)
Failed to attend appointment   (n=3)
Could not make scheduled
appointment   (n=1)
(n=1)

Lost to follow   (n=3)
Failed to attend appointment   (n=1)
Could not make scheduled
appointment   (n=2)

Assessment

Assessed for VISA-A score   (n=13)
Assessed for Tendon Thickness (n=13)
Assessed for Neovascularity   (n=13)

Assessed for VISA-A score   (n=10)
Assessed for Tendon thickness (n=10)
Assessed for Neovascularity   (n=10)

Figure 6.1 illustrates the recruitment flowchart for the study using the CONSORT guidelines

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6.3.5 Adherence with Eccentric Loading Exercise Programme (Control Group)

All subjects randomised to the control group were asked to complete a daily exercise diary (see appendix 5) for the 12-week duration of their exercise programme. Subjects were asked to return the diary at their follow-up appointment. Of the 13 subjects randomised to the control group, nine returned their completed diaries. The other four failed to provide any evidence of adherence during the period of exercise.

As previously discussed in section 4.6 the study followed the Alfredson (1998) protocol which prescribes eccentric loading exercises twice daily for 12-weeks. That is a total of 168 exercise sessions. From the returned diaries the number of sessions carried out by each subject was calculated and then presented as a percentage of the total. The mean percentage adherence was then calculated based on the returned diaries only. In addition, the diaries were reviewed to try and identify any patterns regarding adherence. Table 6.2 illustrates the numbers of sessions completed and as a proportion of all sessions.

Table 6.2 illustrates the mean number of eccentric loading exercise sessions

	Minimum	**Maximum**	**Mean**	**Standard deviation**
Number of exercise sessions completed (maximum = 168)	98	167	125	± 22.4
Number of sessions completed as a percentage of total (168 sessions)	58.3%	99.4%	74%	± 13.4%

The mean number of exercise sessions completed by the subjects was 125 over the 12-week period (74%). The table also illustrates that the number of sessions completed by the group ranged from 58.3% (98 sessions) to 99.4% (167 sessions).

As the HVUGI was a single treatment intervention then subjects in this group were not required to complete adherence dairies.

6.3.6 Adverse reactions

There were no adverse reactions reported in the study. One patient found the injection of saline around the tendon to be very uncomfortable. However, the injection was completed but with a significantly reduced amount of saline (20ml). The patient reported that the discomfort lasted for approximately two hours post-injection.

Some of the subjects, although advised within the patient information sheet (appendix 1) found the eccentric loading exercises painful to do particularly in the first 3-5 weeks.

6.4 Secondary aims

In this study the experimental data were analysed in two ways. Firstly, analyses were performed including all subjects irrespective of whether follow-up data was missing or not (Intention to treat analysis). This was then followed by repeating the analysis after removing those subjects from the sample where follow-up data was missing. The exclusion of subjects where data is missing is referred to as complete case analysis and is considered a recognised method of dealing with the issues of missing data. Although this method can be used with any kind of statistical analysis and requires no special computation, it can exclude a substantial proportion of the original sample especially in studies with multiple variables. A reduction in a study's original sample size can weaken the statistical power of study and lead to biased conclusions (Maxwell et al., 2008). In this study missing data was related to attrition which was discussed earlier in this chapter and methods to try and reduce the levels in any future study discussed in chapter 7. As there was no intention to carry out any hypothesis testing in this study the complete case analysis method of dealing with missing data was considered adequate. However, in a future RCT other methods of dealing with missing data would be considered and statistical advice taken.

6.5 Descriptive Statistics (sample including missing data)

The means, medians, range and standard deviations were, calculated for all the output data from both the control and the treatment group. This would allow some comparisons of means or medians of the outcome measures for this study (i.e. VISA- A score, tendon thickness and neovascularity).

6.5.1 Primary Outcome Measure: VISA–A score (including missing data)

Table 6.3 -Illustrates the mean, median range and standard deviation and interquartile range (IQR) for the VISA- A scores at baseline and post intervention for the control group (Eccentric Loading Exercise programme) and the treatment group (HVUGI)

VISA-A score by groups		N	Min	Max	Mean (±SD)	Median (IQR)
Control Group	**Baseline VISA-A score**	19	8	73	49.58 (17.06)	51.0 (27)
	Post Intervention VISA -A score	13	16	94	64.00 (25.47)	73.0 (44)
Treatment Group	**Baseline VISA-A score**	14	21	85	48.07 (19.78)	46.5 (29)
	Post Intervention VISA -A score	10	30	98	60.80 (22.75)	56.5 (40)

The VISA-A questionnaire measures the domains of pain, functions of daily living and sporting activity. The validity and reliability of its use was discussed in chapter 4.3.1 where we also provide the rationale behind its use as an outcome measure in this thesis. Results range from 0-100, where 100 is the perfect score (i.e. no pain). From table 6. 3 the baseline VISA-A scores were shown to be very similar in both groups with increases in the mean and median scores post intervention suggesting a reduction in pain and improved function following the administration of a HVUGI or completion of the eccentric loading exercise programme. In the control group the mean VISA-A score increased from 49.58 ± 17.06 to 64.0 ± 25.47 with the median increasing from 51 (IQR 27) to 73 (IQR 44). In the trial group the mean VISA–A score increased from 48.07 ± 19.78 to 60.80 ± 22.75 whilst the median increased from 46.5 (IQR 29) to 56.5 (IQR 40).

6.5.2 Secondary Outcome Measure: Achilles tendon thickness in sample including missing data

Table 6.4 Illustrates the mean, median range and standard deviation for the tendon thickness measured in millimetres at baseline and post intervention for the control group (Eccentric Loading Exercise programme) and the treatment group (HVUGI)

Achilles Tendon Thickness (mm)		N	Minimum	Maximum	Mean (± SD)	Median (IQR)
Control Group	Baseline	17	6	16	10.41 (± 2.8)	10.00 (3)
	Postintervention	13	6	14	9.69 (±7.23)	10.00 (5)
Treatment Group	Baseline	13	8	14	11.00 (± 2.00)	11.00 (4)
	Posttreatment	10	8	15	10.50 (± 2.12)	10.00 (3)

One of the clinical features of non-insertional Achilles tendinopathy is thickening of the tendon about 2-6cm from the insertion into the calcaneus. In this study the tendon was measured at its thickest point using the inbuilt measuring tool of the Logiq E9 GE Healthcare diagnostic ultrasound machine and GE 9L probe. The measurement was performed by a Consultant Radiologist with 15 years of experience in musculoskeletal ultrasound. The results in table 4 show that the mean thickness of the Achilles tendon at baseline was very similar in both groups with a reduction noted in both groups post intervention. A reduction in mean tendon thickness from 10.41mm to 9.69mm was found in the control group with no difference recorded in the median of 10mm. In the treatment group a reduction in the mean tendon thickness from 11.00mm to 10.50mm and a reduction in the median thickness from 11.00mm to 10mm was recorded. Although a reduction in tendon thickness was noted in both groups, clinically the Achilles tendons still appeared thickened.

6.5.3 Secondary outcome measures: neovascularity Score (NS 0-4) in sample with missing data

The score for neovascularity was defined as the number of vessels evident on power doppler ultrasound. The scores were recorded at baseline and post intervention in both the control and

treatment groups. The scores range from 0-4 where 4 is associated with severe tendinopathy and 0 a normal tendon. In the control group the mean neovascularity score reduced from 2.12 ± 1.41 to 1.69 ± 1.25 and a median from 2.00 (IQR 3) to 1.00 (IQR 2). In the treatment group the mean score reduced from 3.31± 0.95 to 2.80 ± 1.32 and the median score reduced from 4.00 (IQR 1) to 3.00 (IQR 2). It is important to note that the neovascularity score in the treatment group was higher at baseline than the control group. This variation between the two groups was by chance as the randomisation took place before the ultrasound scanning.

Table 6.5 Illustrates the mean, median, range and standard deviation for the neovascularity score (0-4) at baseline and post intervention for the control group (Eccentric Loading Exercise programme) and the treatment group (HVUGI)

Neovascularity score (NS) (0-4)		N	Minimum	Maximum	Mean (± SD)	Median (IQR)
Control Group	NS baseline	17	0	4	2.12 (± 1.41)	2.00 (3)
	NS postintervention	13	0	4	1.69 (± 1.25)	1.00 (2)
Treatment Group	NS baseline	13	1	4	3.31 (± 0.95)	4.00 (1)
	NS postintervention	10	1	4	2.80 (± 1.32)	3.00 (2)

6.6 Test of Normality in sample including missing data

Normality testing was carried out to establish if the data was normally distributed as this helps guide the researchers to which statistical tests should be performed on the data collected when comparing the groups within the study. The data for the VISA-A scores, neovascularity, and Achilles tendon thickness variables in both the control and treatment groups were tested for normality.

The process adopted for normality testing was twofold. An initial histogram with a superimposed distribution curve was produced for each variable and are available to review in appendix 7. In addition for each variable the data was analysed using a Shapiro Wilks test. This test of normality first described in 1965, rejects the hypothesis of normality when the pvalue is less than or equal to 0.05. Failure of the normality test at this level of significance

states that there is a 95% confidence that the data is not normally distributed. Table 6 below illustrates the p-value for each variable.

Table 6.6 Illustrates the test of normality for the VISA-A, Tendon thickness and neovascularity in both the control and treatment group at baseline and post intervention (including missing data)

Group	Measure		ShapiroWilks	
		Statistic	df	p-value
Control Group	Baseline VISA-A score	0.955	19	0.473
Treatment Group	Baseline VISA-A score	0.956	14	0.651
Control Group	Post intervention VISA-A score	0.905	13	0.156
Treatment Group	Post intervention VISA-A score	0.949	10	0.659
Control Group	Baseline Tendon thickness	0.934	17	0.256
Treatment Group	Baseline Tendon thickness	0.917	13	0.230
Control Group	Post intervention tendon thickness	0.937	13	0.422
Treatment Group	Post intervention tendon thickness	0.891	10	0.173
Control Group	Baseline neovascularity score	0.892	17	0.05
Treatment Group	Baseline neovascularity score	0.753	13	0.002
Control Group	Post intervention neovascularity score	0.908	13	0.174
Treatment Group	Post intervention neovascularity score	0.769	10	0.006

Test of normality

The histogram and distribution curves for the baseline and post intervention measures for the VISA-A score, tendon thickness and neovascularity in both the treatment group and control group are shown in appendix 9. The Shapiro-Wilks test calculated p-values are illustrated in table 6.6 and show that the data for the VISA-A scores, and tendon thickness pre and post intervention in both groups to be greater than 0.05 and were considered normally distributed.

Regarding the neovascularity scores the control group scores was equal to 0.05 and therefore the data was considered normally distributed whilst the level of significance calculated for the trial group was less than 0.05 and as such was considered not to be normally distributed. Post intervention scores for the neovascularity in the control group scores was greater than 0.05 and considered normally distributed whilst the data for the treatment group was less than 0.05 and therefore not considered normally distributed.

6.7 Statistical analysis of sample including missing data

The test for normality identified that the data, except for the neovascularity scores at baseline and post intervention for the treatment group, were normally distributed. This would normally support the use of parametric tests. However, the small sample size used in this study, although considered suitable for a feasibility study, does not meet the size guidelines for parametric tests (Kaur and Kumar 2015). Therefore, it was considered appropriate in this study to analyse the data using non-parametric tests. In any future RCT the sample size would be sufficiently powered as to optimise type I or type II errors, thus giving confidence in the findings of the normality testing to inform the statistical analysis.

The data were analysed using the Wilcoxon signed rank test which is a non- parametric statistical test used to compare two related samples. This test was used to analyse each group individually between baseline and post intervention. The Mann-Whitney U test, a nonparametric statistical test, was used to compare the data between the control and trial groups.

6.7.1 Comparing pre and post-intervention effects on VISA-A, tendon thickness and neovascularity in the control and treatment group using Wilcoxon Signed-Rank Test (in sample including missing data)

The Wilcoxon Signed Rank test allows two sets of scores to be compared from the same participant. It is the non-parametric equivalent of the paired t-test. By analysing the data in the two groups using the Wilcoxon Signed Rank test it is possible to statistically calculate the change in the VISA-A scores, tendon thickness and the neovascularity scores associated with the intervention in the control group (ELE programme) and in the administration of a HVUGI in the treatment group. By analysing the effect of the intervention in each group the results can be reviewed in the context of similar published literature.

The analysis of data is this section includes missing data due to attrition, and as a result included all the measured variables for each subject lost to follow-up. In the control group the number lost to follow up was 5 subjects and 3 in the treatment group.

Table 6.7 illustrates the statistical results when comparing the change in the VISA-A scores, tendon thickness and neovascularity scores within the control and treatment groups (sample including missing data)

Groups		Difference between baseline and post intervention VISA-A scores	Difference between baseline and post intervention tendon thickness	Difference between baseline and post intervention neovascularity score
Control Group	**p-value**	0.017	0.135	0.442
Treatment Group	**p-value**	0.012	0.705	0.071

On the primary outcome measure of the VISA-A score table 6.7 illustrates there is a statistically significant difference between the baseline and post intervention scores in both the control group and treatment group. Using a Wilcoxon Signed Rank Test and a level of significance of ≤ 0.05 there was a significant difference in the VISA-A score in the control (p=0.017) and treatment (p=0.012) groups. The higher post-intervention scores recorded suggest clinical improvement (improved function and reduced pain) with both an ELE programme and a HVUGI.

On the primary outcome measure of tendon thickness Table 6.7 illustrates there was no statistically significant change in the tendon thickness between baseline and post intervention measurements in either the control or treatment groups. Using a Wilcoxon Signed Rank Test and using a level of significance of ≤ 0.05 no significant change in the tendon thickness was found in either the control (p=0.135) or treatment (p=0.705) groups associated with either intervention which suggests that tendon thickness was not affected by an increase in the VISAA score (improved function and reduced pain.)

On the primary outcome measure of the neovascularity Table 6.7 illustrates that there was no statistically significant difference between the pre and post intervention NS in both the control and treatment groups. Using a Wilcoxon Signed Rank Test and a level of significance of ≤ 0.05

there was no significant difference in NS in either the control (p= 0.442) or treatment (p=0.071) groups associated with either intervention which suggests that neovascularity was not affected by an increase in the VISA-A score (improved function and reduced pain).

6.7.2 Comparing the VISA-A score, tendon thickness and neovascularity score between the control group and trial group using the Mann-Whitney U Test (in sample including missing data)

The Mann-Whitney U test is used to compare whether there is a statistical difference in the dependant variables for two independent groups. In this study the dependant variable were the VISA-A scores, neovascularity scores and tendon thickness, whilst the independent groups refer to the control and treatment groups. It is a non-parametric equivalent of the unpaired ttest and is used in hypothesis testing. However, it is important to note that no hypothesis testing was performed as part of this feasibility study due to the small sample size. Therefore, the aim of this phase was to test the analysis methods and interpretation that could be used to assess the effect of HVUGI compared with ELE on the dependant variables.

Table 6.8 illustrates the results of a Mann-Whitney U test to analyse any statistical differences between the control group and treatment group.

	Baseline VISA-A score	Post Intervention VISA -A score	Baseline tendon thickness	Posttreatment tendon thickness	Baseline NS	Post intervention NS
Mann-Whitney U test	123.000	58.500	91.500	52.500	56.000	34.500
Asymp. Sig. (2-tailed)	0.716	0.687	0.423	0.434	0.018	0.051

Table 6.8 illustrates the Mann-Whitney U test used to analyse if there was a significant difference between the control group and treatment group at baseline and post intervention. Using a level of significance of $p \leq 0.05$, no significant difference was noted for the VISA-A score between the trial groups and the control group both at baseline and post intervention. Similarly, there was no statistically significant difference noted for tendon thickness between

the treatment group and control group both at baseline and post intervention. With regards to the neovascularity score there was a significant difference between the groups at baseline, with NS scores higher in the treatment group. Post-treatment the results marginally suggest no difference in NS (p=0.051). A review of the descriptive statistics suggest that the percentage change was similar in both the control and treatment groups.

6.8 Complete case analysis

In the previous section the analysis of data was performed on participants in each group where some of the data were missing. To compensate for the missing data the analysis was performed again only using complete data from participants. This resulted in the sample size being reduced to 11 participants in the control group and 10 participants in the trial group.

6.9 Descriptive Statistics (complete data set)

The means, medians, range and standard deviations were, calculated for all the output data from both the control and the treatment group. This would allow some comparisons of means or medians of the outcome measures for this study (i.e. VISA-A score, tendon thickness and neovascularity).

6.9.1 Primary Outcome Measure: VISA-A using complete data set

Table 6.9 -Illustrates the mean, median, range and standard deviation for the VISA-A scores pre and post intervention for the control group (Eccentric Loading Exercise programme) and the treatment group (HVUGI) for the complete data set.

VISA-A score by groups		N	Minimum	Maximum	Mean (±SD)	Median (IQR)
Control Group	Baseline VISAA score	11	8	69	44.91 (±5.10)	45 (16)
	Post Intervention VISA -A score	11	26	94	66.09 (±21.98)	73 (33)
Treatment Group	Baseline VISAA score	10	21	85	48.50 (±22.16)	48 (41)
	Post Intervention VISA -A score	10	30	98	60.80 (±22.75)	56.50 (40)

Table 6.9 illustrates the descriptive statistics for the VISA-A scores pre and post intervention for the control group and trial group when the samples only include participants for which there is complete baseline and post intervention results. The table shows that when participants with incomplete data are removed the control group consists of 11 participants and the treatment group 10. Table 6.9 also shows an increase in the mean and median VISA-A scores in both groups post intervention. The mean baseline VISA-A scores were within 3.6 points which would be considered similar with regards to the severity of pain and function. In the control group the mean VISA-A score increased from 44.91 ± 5.10 to 66.09 ± 21.16 with the median increasing from 45 (IQR 16) to 73 (IQR 33). In the trial group the mean VISA –A score increased from 48.5 ± 22.16 to 60.80 ± 22.75 whilst the median increased from 48 (IQR 41) to $56.5 \pm$ (IQR 40).

6.9.2 Tendon Thickness (measured in millimetres)

Table 6.10 Illustrates the mean, median range and standard deviation for the tendon thickness measured in millimetres at baseline and post intervention for the control group (Eccentric Loading Exercise programme) and the treatment group (HVUGI) for the complete data set.

Achilles Tendon Thickness (mm)		N	Minimum (mm)	Maximum (mm)	Mean (± SD)	Median (IQR)
Control Group	Baseline	11	6	16	11.00 (± 0.87)	10 (4)
	Posttreatment	11	6	14	10.27 (± 2.49)	10 (5)
Treatment Group	Baseline	10	8	11	10.40 (± 0.58)	11 (3)
	Posttreatment	10	8	15	10.50 (± 2.12)	10 (3)

Table 6.10 illustrates the descriptive statistics for the tendon thickness measured in millimetres both at baseline and post intervention for the control group and the treatment group when the samples only include participants for which there is complete baseline and post intervention results. The table shows that when participants with incomplete data are removed the control group consists of 11 participants and the treatment group 10. Table 10 also shows a decrease

in the mean tendon thickness measurements in the control group from 11mm ± 0.87 to 10.27mm ± 2.49 but no change in the median which was 10mm (IQR 4) at baseline and 10mm (IQR 5) post intervention. In the treatment group a minor increase in the mean tendon thickness was noted from 10.40mm ± 0.58 to 10.50mm ± 2.12 and a decrease in the median from 11mm (IQR 3) to 10mm (IQR 3). The very small changes reported in the mean tendon thickness were not observed on clinical examination, with thickening still evident post intervention in both the treatment and control groups.

6.9.3 Neovascularity Score (measured 0-4)

Table 6.11 Illustrates the mean, median, range and standard deviation for the neovascularity score (0-4) at baseline and post intervention for the control group (Eccentric Loading Exercise programme) and the treatment group (HVUGI) for the complete data set

Neovascularity score by groups (0-4)		N	Minimum score	Maximum score	Mean (± SD)	Median (IQR)
Control Group	NS baseline	11	0	4	2.45 (±1.44)	2.00 (3)
	NS posttreatment	11	1	4	2.00 (±1.1)	2.00 (2)
Treatment Group	NS baseline	10	2	4	3.60 (±0.70)	4.00 (1)
	NS posttreatment	10	1	4	2.80 (± 1.32)	3.00 (3)

Table 6.11 illustrates the descriptive statistics for the neovascularity scores both at baseline and post intervention for the control group and treatment group when the samples only include participants for which there is complete pre and post intervention results. Table 6.11 also shows a decrease in the mean tendon neovascularity score in the control group from 2.45 ± 1.44 to 2.00 ± 1.1 but no change in the median which was 2.00 (IQR 3) at baseline and 2.00 (IQR 2) post intervention. In the trial group the mean neovascularity score calculated decreased from 3.60 ± 0.7 to 2.80 ± 1.32 post intervention and the median also decreased from 4.00 (IQR 1) to 3.00 (IQR 3).

6.10 Test of Normality for complete case analysis

Normality testing was carried out for the complete case analysis and followed the same twofold process as adopted previously in section 6.6. An initial histogram with a superimposed distribution curve was produced for each variable and are available to review in appendix 7. In addition to the histogram and distribution curves generated for each variable the data was analysed using a Shapiro Wilks test. This test of normality first described in 1965, rejects the hypothesis of normality when the p-value is less than or equal to 0.05. Failure of the normality test at this level of significance states that there is a 95% confidence that the data is not normally distributed. Table 6 below illustrates the p-value for each variable.

Table 6.12 illustrates the test of normality for the VISA-A, Tendon thickness and neovascularity in both the control and treatment group at baseline and post intervention for the complete case analysis

Group	Measure		ShapiroWilk	
		Statistic	df	Sig.
Control Group	Baseline VISA-A score	0.945	11	0.584
Treatment Group	Baseline VISA-A score	0.926	10	0.407
Control Group	Post intervention VISA-A score	0.921	11	0.329
Treatment Group	Post intervention VISA-A score	0.949	10	0.659
Control Group	Baseline Tendon thickness	0.888	11	0.131
Treatment Group	Baseline Tendon thickness	0.885	10	0.150
Control Group	Post intervention tendon thickness	0.953	11	0.681
Treatment Group	Post intervention tendon thickness	0.891	10	0.173
Control Group	Baseline neovascularity score	0.879	11	0.102
Treatment Group	Baseline neovascularity score	0.650	10	0.000
Control Group	Post intervention neovascularity score	0.828	11	0.02

Treatment Group	Post intervention neovascularity score	0.769	10	0.006

Test of normality for complete case analysis

The histogram and distribution curves for the baseline and post intervention measures for the VISA-A score, tendon thickness and neovascularity in both the treatment group and control group are shown in appendix 7 The Shapiro-Wilks test calculated p-values are illustrated in table 6.12 and show that the data for the VISA-A scores and tendon thickness pre and post intervention in both groups to be greater than 0.05 and were considered normally distributed. Regarding neovascularity the baseline control group scores were greater than 0.05 and therefore the data was considered normally distributed whilst the treatment group scores were not considered to be normally distributed. The level of significance calculated for both groups post intervention was less than 0.05 and as such were considered not to be normally distributed

6.11 Statistical analysis – complete case analysis

The test for normality performed on the complete data set identified that the VISA-A scores at baseline and post intervention for both groups was normally distributed as was the data pertaining to tendon thickness. However, the neovascularity scores pre-intervention for the trial group and post intervention scores for both the trial group and control group were not normally distributed. As the sample size was reduced in both the control (n=11) and treatment group (n=10) when participants were removed because of incomplete data the use of non-parametric testing was considered appropriate in this study. Therefore, the data were analysed using the Wilcoxon signed rank test which is a non- parametric statistical test used to compare two related samples and used to analyse each group individually pre and post intervention. The Mann-Whitney U test, a non-parametric statistical test, was used to compare the data from the control and trial groups.

6.11.1 Comparing pre and post intervention effect on VISA-A, tendon thickness and neovascularity in the control and trial group using Wilcoxon Signed-Rank Test for the complete data set

The Wilcoxon Signed Rank test allows two sets of scores to be compared from the same participant. It is the non-parametric equivalent of the paired t-test. By analysing the data in the

two groups using the Wilcoxon Signed Rank test it is possible to statistically calculate the change in the VISA-A scores, tendon thickness and the neovascularity scores associated with the intervention in the control group (ELE programme) and in the administration of a HVUGI in the treatment group. By analysing the effect of the intervention in each group the results can be reviewed in the context of similar published literature.

The analysis of data is this section excludes missing data due to attrition, Therefore the analysis included data from 11 subjects in the control group and 10 subjects in the treatment group.

Table 6.13 illustrates the statistical results comparing the changes in the VISA-A scores, tendon thickness, and neovascularity scores within the control and treatment groups - complete case analysis

Groups		Difference between Baseline and post intervention VISA-A scores	Difference between baseline and post intervention tendon thickness	Difference between baseline and post intervention neovascularity score
Control Group	**p-value**	0.016	0.135	0.442
Treatment Group	**p-value**	0.012	0.705	0.071

Statistical Comparison of VISA-A scores at baseline and post intervention in the control and treatment group – complete case analysis.

Table 6.13 illustrates those results from the Wilcoxon Signed –Rank Test. Using a level of significance of ≤ 0.05 there was a statistically significant difference in the VISA-A scores recorded at baseline and post intervention in both groups. In the control group the significance level was 0.016 and in the treatment group 0.012

Statistical comparison of the tendon thickness at baseline and post intervention in the control and treatment groups.

Table 6.13 illustrates whether there is a statistically significant difference in the tendon thickness measured at baseline and post intervention in both the control and treatment groups. Using level of significance of ≤ 0.05 there was no significant difference in the tendon thickness at baseline and post intervention in either the control or trial group. In the control group the significance level was calculated at 0.135 and in the trial group 0.705.

Statistical comparison of Neovascularity Scores at baseline and post intervention in the control and treatment groups

Table 6.13 illustrates whether there is a statistically significant difference in the neovascularity scores measured in both groups at baseline and post intervention. There was not significant difference calculated using a level of significance of ≤ 0.05. In the control group recorded a level of significance was calculated at 0.442 and in the treatment group 0.07

6.11.2 Comparing the VISA-A score, tendon thickness, and neovascularity score between the control groups and trial group using the Mann- Whitney U test- complete case analysis

As previously stated in section 6.7.2 the Mann-Whitney U test is used to compare whether there is a statistical difference in the VISA-A scores, tendon thickness and neovascularity scores for the control and treatment groups. It is a non-parametric equivalent of the unpaired t-test and is used in hypothesis testing. However, it is important to note that no hypothesis testing was performed as part of this feasibility study due to the small sample size. Therefore, the aim of this phase of testing was to describe the effect of HVUGI compared with ELE on the dependant variables.

Table 6.14 Illustrates the results of the Mann-Whitney U test to analyse the statistical differences between the control group and trial group using the complete data set.

	Baseline VISA-A score	Post Intervention VISA -A score	Pretreatment	Posttreatment	NS pretreatment	NS posttreatment
Mann-Whitney U	49.000	47.000	51.000	52.500	29.500	34.500

Asymp. Sig. (2tailed)	.672	.573	.775	.858	.051	.133

Table 6.14 illustrates the Mann-Whitney U test used to analyse the differences between the control group and trial group both pre and post intervention. Using a level of significance of $\leq$ 0.05 no significant difference was noted for the VISA-A score between trial and control groups both pre and post intervention. Similarly there was no statistically significant difference noted for tendon thickness or neovascularity between groups pre and post intervention.

6.12 Sample Size estimate

The data collected pertaining to the PROM (VISA-A) was used to calculate the effect size

Cohen's d = (mean of treatment group) – (mean of control group)

Standard Deviation (pooled)

In the previous calculation the standard deviation refers to that of the population from which the two groups were taken. As this was not calculated in this study, then the pooled standard deviation was calculated and used instead.

SD pooled = $\sqrt{}$ SD² (Trial group) + SD² (Control group)

2

Using the above formula the pooled standard deviation for the study data which included missing data was calculated below

SD pooled = $\sqrt{}$ 25.47² + 22.75²

2

SD pooled = 34

Therefore using 34 as the SD pooled

Cohen's d = 0.1

The calculation was then repeated using the results from the analysis of data from the complete data set.

$$\text{SD pooled} = \frac{\sqrt{21.93^2 + 22.75^2}}{2}$$

SD pooled = 31.6

Therefore using 31.6 as the SD pooled

Cohen's d = 0.2

Using the data from this study the sample effect size was calculated as 0.1. Therefore, calculating sample size from Cohen's table using a power of 0.8, significance level of 0.05 and effect size (d) of 0.1 would require a sample size of 1,571 in each arm of the study. When the effect size (d) was changed to 0.2, as calculated for the complete dataset, the sample was reduced to 393 in each arm.

6.13 Chapter Summary

The focus of this chapter was to analyse the data pertaining to the primary and secondary aims of this study. The primary aims were to evaluate recruitment and retention whilst the secondary aims focused on the experimental phase and analysis of results. The study found during a 6month period 63 patients were referred to the department of orthopaedics in a large Scottish Teaching Hospital with Achilles tendon pain. Of those 43 (68%) were deemed eligible and 33 (77%) agreed to participate in the study. Of the 33 randomised (treatment group =14, control group 19) two were excluded because of abnormal ultrasound scans. Eight subjects were lost to follow-up at 12 weeks resulting in a retention rate of 74% (n=23). Adherence to the eccentric loading programme was 74% when recording the number of exercise sessions completed as a percentage of the total suggested. Although improved function and reduced pain were observed in both groups, reflected by an increase in the mean VISA-A score, no significant difference was noted between the groups. No differences were observed in the secondary physiological measurements of tendon thickness and neovascularity either. However, caution regarding the outcome measures should be exercised due to the small sample size. In chapter 7 we discuss

the results in the context of the research literature whilst identify how these findings might influence future research.

CHAPTER 7 DISCUSSION SECTION

7.1 Introduction

The aim of this thesis was to investigate the feasibility of carrying out a RCT to compare HVUGI (Treatment group) with eccentric loading exercises (Control group) for the management of non-insertional Achilles tendinopathy. A review of the literature in Chapter 4 showed encouraging results in reducing pain and improving function when a HVUGI was administered for the treatment of non-insertional Achilles tendinopathy (Chan et al., 2008, Humphrey et al., 2009, Resteghini and Yeoh 2012, Maffulli et al., 2013, Wheeler 2014, and Gronbech –Nielson et al., 2020). However, there were some methodological weaknesses in these studies with a propensity to adopt a case series approach in athletic populations. This approach challenged the generalisation of the results to a non-athletic population and failed to identify if the administration of a HVUGI is more effective in reducing pain and improving function than an eccentric loading exercise programme, which continues to be the mainstay of non-surgical management.

Eccentric exercise programmes such as those described by Alfredson (1998) and used as the control intervention in this study are long (12 weeks), laborious and painful to perform, therefore raising issues of adherence and thus effectiveness. Adherence to any prescribed treatment intervention is important and can significantly affect the clinical outcome. Several reasons have been highlighted in the literature as potential barriers to patients carrying out prescribed exercises. Dobkin et al., (2006) reported a reduced adherence associated with exercises that patients found painful to perform. Although their programme was of similar duration (12 weeks), it was targeted at women diagnosed with fibromyalgia and contained a combination of stretching and aerobic exercises. Although the reduced adherence reported by Dobkin at al., (2006) was from a specific cohort of patients their findings concur with those from an earlier study by Minor and Brown (1993) who also reported a reduction in exercise adherence when patients living with osteoarthritis were prescribed exercises which they found painful to perform. In addition to the effect of pain on exercise adherence, some patients may find exercise programmes challenging to complete, particularly those who may be overweight

and less physically active (Schoo et al., 2005). A systematic review carried out by Jack et al., (2010) found low levels of physical activity or aerobic capacity at baseline or prior to commencement of treatment as a barrier to exercise adherence. Overall adherence with homebased exercise programmes of relatively long duration and intensity ranges from 47% (McLean et al., 2013) to 71.6% (Kolt 2003), and is considered a barrier to an effective treatment outcome.

Therefore, the PI identified a need to redefine how non-insertional Achilles tendinopathy is treated in non-athletic patients which may facilitate early return to some level of physical activity, whether recreational or work. The use of a single HVUGI could offer the potential as an alternative treatment to a home-based exercise programme which is long, laborious, and often painful to perform. By reducing this period of immobility, the comorbidities associated with inactivity such as obesity, hypertension and reduced aerobic capacity could also be reduced.

In the design of this study reference to the CONSORT (2016) guidance for feasibility studies was made throughout. The guidance suggests that the focus of such a study should ask whether a future trial can be done, should be done and if so how. The primary aims of this thesis therefore were to consider if the trial could and should be done considering aspects such as recruitment and retention of participants. A small-scale version of the proposed definitive RCT was carried out as part of this study with the aims of testing the data collection and analysis techniques that would be considered in a future study. As the sample size was purposely small no hypothesis testing was carried out as part of the analysis, although patterns in the results were recorded and discussed later in this chapter.

7.2 Sample size and information on the sample population

7.2.1 Sample size

Sample size is an important consideration when planning any clinical trial, with sample size calculations used to identify the minimum number of participants required to be able to answer the research question (Whitehead et al 2016). If the sample is too small, then the chance of an inconclusive result is high. If the number of participants is too high, then this results in wasted resources and the chance that many more participants are exposed to a treatment which may be inferior to what might normally be offered. This can raise ethical issues pertaining to unnecessary exposure (Julious and Owen 2009). One of the primary aims of this feasibility

study was to ensure that in planning any future clinical trial the PI could proceed with confidence to recruit sufficient numbers to prevent inconclusive results. This issue of inconclusive results has been highlighted in the Medical Research Council (MRC) guidance document on developing and evaluating complex interventions (Craig et al., 2006). This publication recommends that feasibility and pilot work are key elements of the development process and should be included in any funding application.

It was accepted from the outset that the sample size used in this feasibility study would be too small to identify a relevant treatment effect and therefore the study would be underpowered for such analyses. As a result, hypothesis testing was not considered appropriate. Recruitment and retention were the primary aims of the study and as such the numbers recruited during a set period of time was recorded and reported. However, it is seen as good practice to provide a sample size target to be recruited within a set time frame and that some justification is provided.

Therefore, based on the previous discussions in section 5.6 the intention was to recruit 30 participants over a four-month (16 week) period. This equated to the recruitment of two participants per week which was considered achievable within the constraints made by the Research and Development team of NHS Lothian from whom approval was sort as part of the ethical approval process. This will be discussed in detail later in section 7.3 and provides some indication of projected recruitment rates for a future RCT.

7.2.2 Sample size characteristics

Thirty-three subjects volunteered to take part in the study. Of those, two were withdrawn due to abnormal ultrasound scans and one voluntarily withdrew. The abnormal ultrasound scans included a cyst identified within the Achilles tendon and one which showed calcification at the insertion of the tendon suggestive of concurrent insertional Achilles tendinopathy. Insertional Achilles tendinopathy was one of the identified exclusion criteria for the study. Both participants were referred for further assessment and treatment. One participant voluntary withdrew when randomly allocated to the control intervention, irrespective of being informed of the randomisation process in the information sheet and signing the consent form to confirm their understanding. Subjects were explicitly advised that they could withdraw at any time during this study. This single case was a consequence of the subject having difficulty in performing the eccentric loading exercises resulting in notified withdrawal at week 2.

Of the thirty-three original volunteers 20 were male and 13 were female with a mean age 53.70 years $\pm$ 11.40 years. Randomisation of the sample resulted in 19 subjects being allocated to the control group (Eccentric Loading Exercise programme) and 14 allocated to the treatment group (HVUGI). The control group consisted of 10 males and 9 females with a mean age of

51.21 years $\pm$ 14.73 years (range 34-74 years) whilst the trial group consisted of 10 males and 4 females with a mean age of 55.36 years $\pm$ 11.08 years (33-73 years). The demographics of the sample population in this study were similar to that reported by Sayana and Maffuli (2007) whose study of Achilles tendinopathy in the general population identified a mean age of the males within the study to be 44 years $\pm$ 22.5 and the females to have a mean age of 51 years $\pm$ 25.2 year with slightly more males than females. Mafi et al., (2001) in their study which compared eccentric loading with concentric loading and reported a similar age range with a mean age of 48.1 $\pm$ 9.5 years in the eccentric training group and 48.4 $\pm$ 8.3 years in the concentric training group. These studies had similar age ranges to the epidemiological study by De Jonge et al (2011) who investigated the incidence of Achilles tendinopathy in the general population by reviewing data from the computerised medical records of Dutch GP's. The study reviewed the records of 57,725 patients and found an incidence of 2.35 per 1000 registered patients which equated to about 107 cases of non- insertional Achilles tendinopathy. The average age of those presenting with Achilles tendinopathy was 43.4 years of which only 35% identified a relationship between their injury and a sporting activity. In a more recent study by Albers et al., (2016) the incidence and prevalence of lower extremity tendinopathies was investigated within a Dutch general practice over a one-year period. The study reported an overall incidence rate of 10.52 per 1000 patients with an incident rate for Achilles tendinopathy reported at 2.16, similar to that reported by De Jong et al., (2011). Although the study by Albers (2016) did not break down the mean age for each specific lower extremity tendinopathy, the overall mean age of the tendinopathy patients was 46 years compared with the mean age of the practice population reported as 36 years. The age range of the sample in this feasibility study was comparable with other studies and is considered representative of the incidence of non- insertional Achilles tendinopathy in the general population reported in other geographical locations. Therefore, in considering the future design of an RCT, this study has provided some evidence that the demographics of participants in this study are similar to studies carried out in other parts of the UK and in Northern Europe.

7.3 Recruitment

7.3.1 Study Design

The proposed plan was to recruit 30 participants in a four -month period. As part of the approval process, both ethical and local Research and Development (R&D) approval was required. The R&D approval process includes a review of both the staff and material resources required to conduct the study. In addition, they overview all research activity being carried out within the health board ensuring no duplication of studies whilst assessing the effect on overall service delivery. As no funding was available the study was conducted within the confines of normal service delivery. It was agreed as part of the R&D approval process that the consultant radiologist who had agreed to take part in the study would have one session per week allocated to the project (three hours). This was approved as part of their work plan and was coordinated to ensure that there was adequate clinical space available including diagnostic ultrasound equipment which was needed to measure tendon thickness, neovascularity and the administration of the HVUGI. In planning the resource allocation, it was important to include both the recruitment period and the review period, which for this study extended to approximately seven months.

It was estimated that within the allocated three-hour session a maximum of three participants could consent, be randomised, have an ultrasound scan and receive the treatment intervention whether that was the administration of the HVUGI or be provided with the proper guidance on the eccentric loading exercise plan. Therefore, the capacity of three participants and a recruitment period of four months should have provided adequate capacity for any lag that could occur between screening and enrolment. At the 12-week point if the recruitment target had not been reached then the session would be a mix between new participants and reviews with the intent of reaching the sample target of 30 whilst reviewing participants at 12 weeks post baseline assessment / intervention.

7.3.2 Recruitment of Participants (Actual)

Unfortunately, the work plan originally agreed by R&D was subject to some changes, which impacted on the recruitment of participants. From a practical perspective, the consultant radiologist was not available for several the scheduled sessions due to annual leave and other work commitments. In addition, at the start of month three of the data collection period the work plan of the consultant radiologist was revised to address staff shortages and increased

waiting times. As a result, the original planned three-hour session was reduced to one hour and was scheduled to take place between 8am and 9am. Consequently, recruitment was reduced to one new patient per week (instead of three) or two 12-week reviews. The reduction in capacity required an extension to the study period which was approved by R&D.

The impact of these revised changes was to extend the overall study period to 10 months (6month) period for recruitment plus 4 months for the 12-week review). As enrolment into the study was not reduced, some lag was created between enrolment and randomisation / allocation which did raise some concerns with patients who had agreed to participate. The retention of subjects in the study was also affected as some participants were unable to attend the early morning appointments due to other commitments and public transport issues. The impact on retention will be discussed later in section 7.3.4. However, within the revised 6month period the study was able to recruit the target sample of 30 (n= 33). Of the 43 patients assessed for eligibility, 10 (23%) declined to take part due to the revised scheduling issues.

The eligibility rate was defined as the number of eligible subjects as a proportion of the total screened patients. During the six-month recruitment period 63 patients were referred to the department of orthopaedics with Achilles tendon pain and screened for eligibility. Of those, 20 were excluded due to fulfilling exclusion criteria which included receiving previous treatment (n=8), bilateral presentation (n=7) and a diagnosis of insertional Achilles tendinopathy (n=5). Therefore 43 subjects were eligible for enrolment into the study equating to an eligibility rate of 68%. This eligibility rate was directly affected by the recruitment process which relied on triaging of patients referred to the department of orthopaedics and the information provided on the referral letter. This information was often vague and as such important exclusion criteria were not identified resulting in 32% of screened patients being excluded. Recruitment relied exclusively on triaging with no promotion of the study within primary care.

In any future trial promotional information would be provided to both general practices and extended to include musculoskeletal teams based in primary care. This would increase the number of referral pathways which would be expected to increase recruitment numbers. BellSayer et al., (2011) identified a number of barriers to recruiting into prospective studies from general practice. These included time pressures, an individual clinician's interest in the specific area of medicine and complicated recruitment material. Unfortunately, researchers

have no control over time pressures in general practice or primary care but can ensure that any information provided to promote recruitment is easy to follow and not onerous to complete.

It is anticipated the promotion of any future trial would also increase the overall recruitment rates. However, it is important to note that if the numbers recruited are increased then the capacity to screen, enrol, randomise and carry out the necessary ultrasound scans and administer the HVUGI would also need to be increased. Consequently, there would need to be an increase in those screening for eligibility. In this study the screening was carried out by a specialist podiatrist employed on a 0.5 WTE (Whole Time Equivalent). As no funding was available, this was carried out in a normal outpatient clinic where 30 minutes was allocated for screening, which equated to the time allocated for a new patient appointment. If funding was available in a future study, then time allocation for screening could be planned and as such increase capacity to accommodate any increases in recruitment because of promoting the study and extending the recruitment pathways.

It is estimated that if a specialist podiatrist was funded for a three-hour session, then a maximum of six patients could be screened during this period (30 minutes per patient). The availability of a consultant radiologist would also need to be increased. In the early phases of this feasibility study, when the consultant radiologist was available for three hours, three new participants could be seen each session up to 12 weeks (rate of 3 per week). If the availability of the consultant radiologist was increased to two sessions per week, then the potential to increase the number of participants would be increased to a maximum rate of six per week for the first 12 weeks and reduced accordingly to manage the 12-week follow ups. The review appointments in this study took 30 minutes per participant, therefore one session could continue to be used to see newly recruited participants whilst the other session could be used to review up to six participants. Overall, in the same period originally allocated for the feasibility study (four months) a maximum of 84 patients could be recruited into the study and reviewed within the added three months. Increasing the study time to two session per week would provide significantly more flexibility for screening and reviewing of participants. This should improve recruitment and retention in a future RCT and is discussed later in section 7.3.3.and 7.3.4.

7.3.3 Recruitment rate

The importance of a study meeting its target sample size is imperative in an RCT and the reason recruitment is a key element and a primary outcome in feasibility studies. Nayak (2010)

suggested that a small sample size will give a result that is not sufficiently powered to detect a difference between the groups, leading to the possibility of a type II error. This type of error in statistics is also known as a false negative and occurs when a researcher does not reject a null hypothesis which is false. A type II error can be safeguarded against by ensuring the sample size is sufficient to detect the difference between the groups.

The importance of recruiting a study's target sample was highlighted by a systematic review carried out by Walters et al., (2017) who reported on the recruitment rates of 151 RCTs between January 2004 and April 2016. The authors reported a median recruitment rate of 0.92 participants per centre per month with an Inter Quartile Range of 2.36 and an overall range between 0.04 and 57.57. The study reported only 63% (95/151) of the studies demonstrated complete compliance with CONSORT guidelines on reporting recruitment information, leading to variation in reporting and the possibility of underestimation of recruitment rates calculated in their study. Based on the limitations of the data extracted only 56% (85/151) achieved the target sample size. This concurs with an earlier study carried out by Sully et al., (2013) who reported 55% (40/73) of 73 trials conducted between 2002-2008 were able to recruit their proposed target sample size. This failure to recruit the target sample size in over 40% of studies described by Walters et al., (2017) and Sully et al., (2013) emphasises the need for feasibility studies to be carried out prior to embarking on a RCT. This should not only inform the feasibility of recruiting sufficient subjects but also provide some indication of the time duration of the data collection phase of any future trial.

In our study the recruitment rate was defined as the number of recruited patients as a proportion of the number of eligible patients (expressed as a percentage). As previously discussed, the number of eligible patients in this study was 43 and of those 10 declined to participate, giving a recruitment rate of 77% (n=33). Of those 10 patients, six declined as they could not attend on the scheduled times. Two declined as they did not wish to risk being randomised into the exercise group as they had expectation of receiving some surgical intervention or to be referred for a HVUGI (declined when the randomisation process was clarified by the PI). The final two patients had needle phobia and therefore refused to participate in the chance they would be randomised into the HVUGI group. In addition to providing a recruitment rate as a percentage of those eligible it is also common practice in the literature to provide the recruitment rate as the number of patients recruited per month.

Therefore, taking cognisance of this alternative method of reporting the recruitment of 33 patients over a 6-month period equated to a rate of 5.5 patients per month.

Artz et al., (2017) assessed the feasibility of carrying out a RCT to compare group-based outpatient physiotherapy with usual care following total knee replacement. They reported a recruitment rate of 37% based on 124 patients being assessed for eligibility. Of the 124 eligible for inclusion in the study 78 (63%) were excluded. Of those 78 excluded, 72 declined to participate with 54% of those citing travelling distance, transportation and commitment to attend as reasons to decline participation. From the study they calculated that a future RCT would require a sample size of 256 patients. Based on their reported recruitment rate of 34%, which equates to the recruitment of 5.75 patients per month (8-month recruitment period), then a recruitment period would need to be extended to 3.7 years to reach their sample target.

In a similar study conducted by Minns Lowe et al., (2012) 107 participants from 181 eligible participants were randomised into two groups. This equated to a recruitment rate of 59.1% (8.2 patients per month) over a 13-month period. Again, the overall recruitment rate was less than reported in this study but was greater when evaluated by the number of patients per month. These study findings highlight possible discrepancies in the recruitment levels dependant on the reporting mechanism and is influenced by the population from which the sample is drawn, and the sample size recruited. A study which has high numbers of eligible patients with a high exclusion rate can still achieve a high numbers of participants per month. Therefore, it is important that both the percentage recruitment and participants per month rates are recorded in feasibility studies and will help planning the resources for a future study.

As previously discussed, the 10 patients who declined to take part in our study because of appointment scheduling constituted 23% of those eligible to take part in the study. By providing more flexibility in appointment scheduling in a future trial could improve the reported recruitment rate further. If, for example, the six patients who declined because of appointment scheduling was reduced to three (50%) then this would increase the recruitment rate from 77% (33 out of 43) to 84% (36 out of 43).

The recruitment rates reported in our study would be considered an adequate level when compared with other studies and would give the PI confidence that a suitable sample size could be achieved in a future RCT. The actual sample size requirements and thus the recruitment period based on the reported recruitment rates will be discussed later in section 7.4.

7.3.4 Retention of subjects / attrition

Attrition is a key consideration when designing an RCT and was quantitatively reported as a primary aim in this study. The attrition rate was calculated to inform the sample size estimate for a future RCT. If attrition is not taken into consideration, then there is a possibility that the RCT could be underpowered and again raise the issues of type II bias. In addition, loss of subjects to follow-up can also introduce bias by altering the characteristics between the randomised groups (Dumville et al., 2006). It may also leave some questions unanswered pertaining to the intervention and any adverse reaction if subjects are lost to follow-up.

Of the 31 subjects that entered our study (18 in the control group and 13 in the treatment group), eight subjects were lost to follow-up equating to 26% attrition. One subject voluntarily withdrew within two weeks of being recruited into the study stating that they did not feel able to do the eccentric loading exercise plan prescribed. They were referred for follow-up treatment out with the study. Three failed to respond to follow-up appointment requests and four stated that they could not make the early morning review appointment imposed because of the reduced availability of the consultant radiologist. Schulz and Grimes (2002) suggest that where attrition is greater than 20% there is concern about the possibility of bias. Therefore, an understanding of why subjects were lost to follow-up in our study is imperative for future planning. The aim would be to reduce attrition to below 20% in any future RCT.

If we consider the nature of those lost to follow-up, four were contacted but were unable to make the early morning follow-up appointment. They did not give any other reason for not attending. Although attempts were made to contact the other three subjects, both by telephone and by letter, no response was obtained. If there had been some flexibility in the appointment scheduling the four contacted who were unable to attend the early morning review appointments could have been scheduled and not lost to follow-up. It would be considered reasonable to assume that more flexibility in the 12-week review appointment scheduling not restricted to before 9am could have reduced the attrition rate to below 20%.

7.4 Sample size estimate

It is imperative that an accurate estimate of sample size is calculated to ensure that the main RCT is suitably powered. The power of a test is the ability to identify correctly that there is a difference between groups in a trial. According to Anthony (1999) it is the ability of a test to reject the null hypothesis when it should be rejected. According to Machin et al., (1997) the

minimum power of 0.8 or 80% is commonly chosen in clinical trials. By selecting this minimum power, the assumption is made that the researchers will accept a 1 in 5 chance that there is no difference between interventions when there is one. In addition to fixing the acceptable level of power it is also important to establish the level of significance α (alpha). The level of significance relates to the critical value chosen for the probability that the null hypothesis is true. According to Devane et al., (2004) the conventional level for alpha is 0.05 (5%), which accepts a 5% probability of falsely rejecting the null hypothesis.

The other variable needed in calculating the sample size is effect size. Freidman et al. (1998) describes the effect size as the magnitude of the difference between two groups that would be regarded as clinically meaningful. They report that this should be pre-specified and can be calculated from a feasibility / pilot study. It is important to note that the larger the effect size the smaller the sample, and the smaller the effect size the larger the sample, assuming the level of significance and power remain constant.

Another term used in the literature to describe effect size is to describe it as the Minimum Clinically Important Difference (MCID). MICD is defined as the smallest change on the scale that would be considered important to a patient and allows clinicians /researchers to evaluate pre and post outcome score and the impact of those scores on the patient's symptoms. In a study conducted by McCormack et al., (2015) a MCID of 6.5 points was the identified level, somewhat lower than previous studies which have estimated it to be between 12 and 20 points (Tumilty et al., 2008, Inversen et al., 2012).

Cohen (1998) defined the effect size as small (0.2), medium (0.5) and large (0.8) when considering a study with two independent samples. Using the data from this study the sample effect size was calculated as 0.1   Therefore, calculating sample size from Cohen's table using a power of 0.8, significance level of 0.05 and effect size (d) of 0.1 would require a sample size of 1,571 in each arm of the study. When the effect size (d) was changed to 0.2, as calculated for the dataset with subjects with missing data removed, then the sample was reduced to 393 in each arm. Therefore, considering the sample size estimates generated from this feasibility study using the above calculation methods, would question the feasibility of carrying out a full-scale trial. The recruitment of 786 participants that fulfil the inclusion and exclusion criteria (396 in each arm) could be challenging to recruit and would require a recruitment period that could extend well in excess of 2 years if basing figures on a single

centred study. However, it might be possible if the recruitment pathways are increased as discussed in section 7.3.2 and the trial extended to include more than one centre.

Authors have warned against using pilot data to calculate effect size (Sim 2019) and the sample size calculations from this feasibility study's data would support that caution. Therefore, we adopted the rule of thumb method described by Cohen (1998) and used a medium effect size (d) of 0.5 which reduced the sample to 64 in each arm (power level of 0.8 and a level of significance of 0.05). This sample size would be feasible to carry out based on the recruitment and retention reported in this study. As part of the process in adopting a medium effect size the literature was reviewed to establish if taking such an approach would be realistic. The review identified that very few Achilles tendinopathy trials reported either the effect size used in the sample size calculation or reported the effect size. In a RCT carried out by Stevens and Tan (2014) which compared the Alfredson Protocol with a lower repetition protocol the effect size reported was 0.42 when the MCID was set at 15 points. In a more recent study by Habets et al., (2017) the sample size was calculated using the analysis from two RCT's by Rompe et al., (2009) and Silbernagel et al., (2007) which calculated an effect size of 0.64 and a MCID of 10 points on the VISA-A scale. If the average effect size of the two studies is considered, then the use of 0.5 would be considered realistic for evaluating the sample size for a future RCT. Although it is acknowledged that in addition to the VISA-A scores, tendon thickness and the neovascularity scores were also recorded and analysed, it is the effect on pain and function measured by the VISA-A which is most important to patients. However, from a research perspective understanding the effect of treatment intervention on these physiological measures will contribute to our understanding of tendon pathology.

7.5 Summary of sample size recommendation

Sections 7.1-7.4 have discussed issues pertaining to the recruitment and retention of participants in this feasibility study. The findings have help inform the projected sample size and recruitment levels for a future RCT. Table 7.1 illustrates the planned and actual recruitment in the study and the reasons for the variation in the two rates have been discussed previously and were likely to be attributed to the reduced availability of the consultant radiologist.

Table 7.1   Recruitment rates for feasibility study and proposed RCT

Study Phase	Recruitment rate	Reasoning
Planned feasibility study recruitment	30 participants in 4-month (17.3 week) period. Approximate recruitment rate per month of 7.5 which equates to 1.7 per week. (Based on one clinical session per week of 3 hours).	
Actual feasibility study recruitment	33 participants in 6-month (26 week) period. Approximate recruitment rate of 1.3 per week.	Result of reduced availability of Consultant Radiologist
Theoretical main RCT recruitment	Based on increasing recruitment to two clinical session per week (6 hours). 128 participants in a 5.6month period (24-week period). Approximate recruitment rate of 5.2 per week with no subjects lost to follow up	Based on calculated sample size of 128 and recruitment of 6 participants per week for 12 weeks (n=72) reducing to 3 per week at the 12-week point (n=12) when 12-week review appointments require scheduling
Proposed main RCT recruitment	128 participants (calculated sample size) plus 25 participants to accommodate 20% attrition rate results in a target sample size of 153 in a 13.7-month period (59 weeks) When the enrolment and randomisation is increased from one three-hour session to two threehour sessions	Based on the actual recruitment rate reported in this feasibility study 2.6 per week (1.3 x 2 sessions equating to 6 hours.)

The effect size as described by Cohen (1998) was estimated as a medium effect size as the effect size calculated from the small sample size resulted in an exceptionally large sample size which would not be possible for any future RCT. Therefore, using the effect size (Cohens d) of 0.5, the sample size was calculated at 128 (64 in each arm of the study). Allowing for a

20% attrition then the recruitment sample target would be 153. With a projected recruitment rate of 2.6 participants per week then the recruitment period is estimated to be 59 weeks (13.7 months). Based on the recruitment and retention in this feasibility study, a larger RCT would be feasible with these alterations to the recruitment process

7.6 Randomisation Process

This feasibility study aimed to randomly assign participants into two groups and evaluate a method of randomisation which could be used in a future RCT. As previously discussed, one group received the HVUGI (experimental group) and the other group acted as an experimental control carrying out eccentric loading exercises. The randomisation was performed using an online randomisation programme (Sealed Envelope). This system is tried and tested and has been used extensively by Higher Education institutions both in the UK and abroad, NHS Boards as well as the MRC Trials Unit. No funding was available for this study and Sealed Envelope provide 50 randomisations for free which was another consideration when choosing a system to use in this study.

The aim of randomising the participants was to achieve similarity of baseline characteristics in both groups. Failure to do this can result in different baseline characteristics which can have confounding effects on the outcome of the study thus challenging what effect the intervention had on both the Patient Reported Outcome Measures (PROMs) and other physical characteristics measured (Sedgwick 2011). Confounding factors can include issues around demographics, such as age and gender, as well as prognostic factors and those characteristics which may influence participation and compliance. In addition to ensuring baseline characteristics, randomisation should also ensure a balance of numbers between groups.

Block randomisation was used in this study to allocate patients to the two groups. Block sizes of four, six and eight were used. The decision to use random block sizes were to reduce the predictability and possible selection bias that can occur when using a single block size (Efird 2011). The randomisation process allocated 33 participants to either to either the control or treatment arm of the study with a total of 34 randomisations carried out (1 trial randomisation was performed at the start of the study).

An imbalance in the numbers allocated to each arm of the trial was seen, with the process randomising 19 participants to the control group and 14 to the trial group. One possible explanation for this is that the sample size was set at 50 with Sealed Envelope rather than reducing it to reflect the proposed sample size of thirty. This combined with the randomised

block sizes of 4, 6, and 8 could be responsible for the discrepancy in the group sizes after carrying out 34 randomisations. However, Schulz and Grimes (2002) challenged the idea that randomised trials need to yield equal groups and even suggested that this can lead to bias by reducing the unpredictability of the assignment of subjects to treatment groups. Therefore, in the context of this study the unequal numbers in each arm are acceptable and the use of block randomisation in a future study should be monitored carefully.

The intention for a future trial would be to use the online randomisation programme (sealed envelope). The general process of randomisation using this online programme was simple and easy to use. The imbalance experienced in this study, although considered acceptable, might be addressed by setting the sample size at the previously projected number of 153 using block randomisation with block sizes of four, six and eight. Regular monitoring of the balance across the groups would be carried out to ensure that the sample size in each arm were similar.

7.7 Adherence with eccentric loading exercise programme

The World Health Organisation (2003) defines adherence as the extent to which a patient follows recommendations agreed with the provider. It is considered vital where an intervention contains unsupervised home-based therapeutic activities (Frost et al., 2016). If the effectiveness of these home-based exercise programmes is to be proven, then understanding the level of adherence is key. This feasibility study used the eccentric loading exercise programme described by Alfredson et al. (1998) as the control group. The idea of not providing any intervention for subjects who were experiencing pain could be considered unethical and a potential barrier to recruitment into a randomised trial. The decision to use the eccentric loading exercise programme as the control reflects its standard use in practice and as such comparisons with this programme should be drawn when evaluating any new treatment. As previously described in section 5.8 it is a home-based exercise programme that is long, laborious and the exercises sometimes painful to perform. It has been shown to provide variable short- and long-term results with Mafi et al., (2001) reporting 82% of athletes in their study returning to pre-injury levels of activity following completion whilst only 54% of nonathletic patients in Sayana and Maffulli (2007) improved to a level where they required no further treatment. It is not intuitive to perform exercises which are painful to perform particularly as part of a rehabilitation programme and highlights the importance establishing the level of adherence. Sacket (1979) reported that poor adherence to unsupervised homebased exercise programmes could be considered ineffective when in reality it is due to an insufficient

regime effect. Martin et al., (2005) suggested that self- reporting can lead to both under- and over-estimation of how much exercise a patient might perform. In addition, they also identified that an individual's beliefs and attitudes could influence adherence to an exercise programme. From a pragmatic perspective, if adherence to a programme with the characteristics described by Alfredson (1998) is poor then its value as a therapeutic intervention might well be questioned and responsible for the variable results

In this feasibility study the adherence with the exercise programme was evaluated with the use of an adherence diary which the participants (randomised to the control group) were asked to complete every day. In a systematic review carried out by Bollen et al., (2014) adherence diaries were reported to be the most common method used to measure self- reported adherence to prescribed home based rehabilitation exercises. Participants in our study were asked to record if they completed the exercises and how many sets and repetitions in each session. By doing this it was possible to record the frequency (number of sessions per week) and the intensity (number of repetitions per session). Mean adherence was measured as the number of sessions completed as a percentage of the total. A session was deemed completed if the participant performed three sets of each exercise even if they were unable to manage the full 15 repetitions. Return rate for the diaries was 69%. Mean adherence was calculated at 74% (Minimum 58.3% Maximum 99.4%).

The relationship between adherence and improvements in the VISA-A score was reviewed but no patterns were evident which might suggest a positive correlation between the VISA-A score and increased adherence. However, it is important to exercise caution regarding the findings in this study the findings were bases on a small sample and an even smaller number of returned diaries.

A review of the literature identified very few studies which reported on adherence rates. In the study conducted by Sayana and Maffulli (2006) patients were informed that they needed to complete at least 75% of the prescribed sets and repetitions to be effective, although no evidence was given to support this level of adherence. The study reported an adherence rate of $81 \pm 7\%$. It was interesting to note the strategies the authors employed to ensure adherence to the exercise programme. Participants in the study were monitored every two weeks in an outpatient clinic, where their compliance data was collected and recorded. In addition, each participant received a weekly telephone call from a research nurse to check adherence to the

exercise programme. With a sample size of 34 participants the level of monitoring used in this study was possible but might be challenging in a study with a much bigger sample size.

Roos et al., (2004), in their study that compared eccentric loading, eccentric loading plus night splint and a third group which just wore a night splint. The study reported 75% (n=24) compliance with the eccentric loading exercises in both groups was considered the desired level for "good compliance". Utilising compliance diaries they recorded declines in compliance over a 13-week period, peaking at 80% at weeks 2-7 before declining to 50% in week 13. Roos et al., (2004) did not find any association between compliance and outcome. If 75% is considered the threshold regarding satisfactory adherence, then adherence in our feasibility fell just short at 74%. Therefore, some method of improving adherence might be considered for a future RCT. It would not be feasible to adopt the strategies employed by Sayana and Maffulli (2007) as the economic impact associated with significant increases in the number of review appointment needed would be considerable.

Text messaging is used extensively in all areas of healthcare to remind patients of appointment times or when they are due review appointments or health checks. According to Abroms et al., (2015) text messaging-based programmes (SMS) on mobile phones can help people modify health behaviours and cites its use in medication adherence, smoking cessation, diabetes management and weight loss. Text messages are usually sent by automated systems and are likely to be read within minutes of being received in contrast to information sent in the post. Chen et al., (2017) used text messaging to encourage patients with frozen shoulders to carry out the prescribed exercises. They conducted a RCT and found that the intervention group which received regular text messaging every day for two weeks reported higher compliance than the control group, which translated clinically to an increase in shoulder function.

The results pertaining to adherence in this study should be viewed with caution because of the small number of returned diaries from a small sample size. Although we are unable to establish with any confidence the overall adherence rate to the eccentric loading exercise programme in this study, from the data analysed it would seem low and with an exercise programme with such a long duration (12 weeks) it would seem prudent to provide some method of reminding / encouraging participants in a future RCT. Therefore, the intention would be to continue with the adherence diaries for participants to complete, but also to provide text messaging at 2week intervals throughout the 12 weeks to encourage participants to carry out the exercises.

7.8 Adverse Reactions

Edwards and Aronson (2000) define an adverse drug reaction as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment or alteration of the dosage regime, or withdrawal of the product". As the treatment arm of this study included the injection of a combination of local anaesthesia and injectable saline, it was important to identify and record any adverse reactions that participants reported. Although no allergic reactions to a subcutaneous injection of saline could be found in the literature the inclusion of local anaesthesia raises the risk of allergic reaction and possible anaphylaxis. In addition, a small number of people can experience a post-injection infection at the site of administration but is minimised by preparing the skin at the site of injection with a single use swab containing 70% alcohol.

Sambrook et al. (2011) reported that allergic reactions to local anaesthetic are uncommon and that many adverse effects are a result of psychogenic responses and reactions unrelated to the anaesthetic agent itself. They identified substances such as adrenaline and preservatives added to the local anaesthetic as a cause of any adverse reaction. Malinovsky et al., (2016) in concurring with Sambrook et al., (2011) reported that the most serious adverse reactions occur because of systemic toxicity which affects both the central nervous and cardiovascular systems. Toxicity can occur because of an excessive dose or unintended intravascular injection. Irrespective of whether the cause of allergic reactions is a result of the local anaesthetic, the preservatives or other additives, it is important to note that all local anaesthetics are supplied with added preservatives and therefore the risk, although low, is still possible. The addition of adrenaline to the local anaesthetic is optional and is commonly used in dental practice to provide local vasoconstriction around the gum. It is not generally used in podiatric practice because vasoconstriction around the toes can result in ischaemia.

In this study, local anaesthetic with no adrenaline was used. Toxicity was guarded against by ensuring the dose of anaesthetic administered did not exceed the maximum safe dose of 200mg (BNF 2020) and that prior to administrating the local anaesthetic and injectable saline aspiration was performed to prevent inadvertently injecting into a blood vessel. In addition, patients with known allergies to local anaesthesia were excluded from the study to again reduce any known risk of allergic reaction (see section 5.3.1 exclusion criteria). A Doppler

ultrasound scan performed on all participants confirmed the clinical diagnosis of noninsertional Achilles tendinopathy and also identified any finding which are contraindicated for the administration of a HVUGI or performing an eccentric loading exercise plan (control in this study) such as partial / complete tear of the Achilles tendon or other abnormal findings. Following the Doppler ultrasound scan performed at baseline, two subjects were withdrawn from the study, one as a result of a large cyst and one for concurrent insertional Achilles tendinopathy. As a precaution, adrenaline was available in case any patients displayed the clinical signs or symptoms of anaphylaxis.

Of the 14 subjects who received the HVUGI no adverse reactions were recorded during or post-injection. One subject reported that the administration of the saline around the tendon was uncomfortable and requested that the consultant radiologist stop the procedure before administering the full 40ml. The subject reported that it made them feel a "little nauseous" however this subsided as soon as the administration of the saline was suspended. This subject was followed up 24 hours later and they reported no lasting adverse effects to the treatment.

With regards to adverse effects the finding of this study concurred with other studies which have evaluated the effectiveness of HVUGI. In the study by Chan et al., (2008) no complications were reported following the administration of a HVUGI in 30 patients. Resteghini and Yeoh (2012) did not report any significant post-injection complications other than some immediate post-injection discomfort. In Resteghini and Yeoh (2012) the anaesthetic was administered mixed with the saline and corticosteroid and as such would not have had any effect immediately following administration. In this study the local anaesthetic was administered prior to the administration of the injectable saline and as such may have reduced some of the immediate post-injection pain. Maffulli et al., (2013) also recorded no adverse reactions to the administration of a HVUGI. It would appear the careful screening of patients including baseline Doppler ultrasound scanning as well as the safety precautions pertaining to the administration of the injection has served to render this a safe method of treatment for non-insertional Achilles tendinopathy. With regards to the eccentric loading exercise programme no adverse effects were noted in this study, other than the expected pain when performing the exercises. Careful screening of the subjects was effective in this study in ensuring no adverse reactions to either intervention.

Therefore, the method adopted in this study, including the screening and composition of the injection, was considered safe with minimal risk of adverse reactions. As a result, the injection

process trailed in this study could be adopted in any future trial. Although the screening process was effective in reducing adverse effects in this study, there is always a possibility that the screening process does not exclude a subject who may have an unknown allergy to local anaesthesia. Consequently, adrenaline and access to the hospital resuscitation team was available to the consultant radiologist in case of an anaphylactic shock. Any future trial should ensure that these safety measures are available to those researchers administering the HVUGI.

7.9. Secondary outcome measures in this study

As part of the feasibility study data were collected pertaining to the VISA- A scores, tendon thickness, and neovascularity scores at baseline and 12 weeks post-intervention for both the control and treatment groups. McGrath (2013) reported that as feasibility/pilot studies are often underpowered due to the small sample size and analysis of data can only be used to generate beliefs that there will be a possible trend towards significance and thus provide support for a future larger study. In evaluating the data, it is important to acknowledge that the main aim of this feasibility study was not to test treatment effectiveness but allow processes to be tested under trial conditions. Taking cognisance of the previous guidance provided by Lancaster (2015) and Thabane et al (2010) no hypothesis testing was carried out in this study as the sample size was small (n=31) and as such the study might be considered underpowered. The expectation is that any future RCT would be suitably powered (as previously discussed in section 7.5) and hypothesis testing would form part of the overall data analysis.

7.9.1 Patient reported Outcomes measures (VISA –A)

The main presenting symptoms with patients with non-insertional Achilles tendinopathy is pain and loss of function, and the VISA-A is the PROM utilised in both the clinical and research arenas. First described by Robertson et al., (2001) it consists of eight questions which measure pain, function in daily living and sporting activity. The introduction of a questionnaire specific to Achilles tendinopathy was a major milestone in being able to draw comparisons to treatment interventions for the management of Achilles tendinopathy. Prior to its introduction the lack of a standardised outcome measure had been considered a major factor in the limited efficacy studies in Achilles tendon research (Khan and Maffulli 1998). As previously described in chapter 4 it is an inverted numerical scale and results in a score of 0100 where an asymptomatic subject would score 100. The decision to use the VISA-A scale in this study was twofold. For one it is a valid and reliable tool and two, has garnered universal

acceptance in the Achilles tendon research field since its introduction. As the previous HVUGI studies have all utilised the VISA-A questionnaire then its use in this study and any future RCT will allow comparisons to be drawn with current published literature. However, it is important to note that the validity and reliability study carried out by Robinson et al., (2001) were performed on those actively engaged in sporting activities and therefore some limitations may exist when administering to the general population.

The following observations were made in this study regarding the use of the VISA-A questionnaire. The administration of the questionnaire at both baseline and 12 weeks were carried out with a researcher in attendance. Although the researcher left the participant to complete the questionnaire on their own, the researcher did, when asked, help clarify any issues pertaining to comprehension of the questions. It is acknowledged that this could have resulted in attention bias but only clarification was offered if asked and the participant left to complete the questionnaire on their own. A number of issues were identified with its use and easily remedied at the time. Some subjects were not familiar with the term "normal gait cycle" and this needed to be explained in lay terms. Subjects were unable to identify the number of single heel raises and single leg hop asked in question 5 and 6 respectively. Although with guidance from the PI all subjects were able to perform the single heel raises which enabled completion of the questionnaire. Some subjects found the single leg hops difficult and challenging to do on either the injured or asymptomatic leg. Question 7 and 8 were based around undertaking sport or physical activity and again an explanation was needed to guide the subjects appropriately.

Mallows et al., (2017) identified a number of issues with the VISA-A. They identified that the physical activity / sporting activity of the questionnaire was worth 40/100 points and as such high functioning individuals might perform irrespective of the pain thus giving a false impression of the degree of disability associated with their Achilles tendinopathy. In addition, the validity and reliability studies carried out by Robinson et al., (2001) were performed on physically active subjects who actively took part in sport. Therefore, its reliability pertaining to the general population might be questioned and improvement in this group might occur at a much lower score.

The VISA-A questionnaire continues to be the universally accepted PROM for the evaluation of non-insertional Achilles tendinopathy and is likely to be utilised for the foreseeable future.

However, from the experiences of administering the VISA-A questionnaire to predominantly non-athletic subjects in this study guidance regarding the comprehension of the questions as well as providing illustrations on how to perform the single heel raise and single leg hops would be useful in any future trial. Although single heel raises and single leg hops are understood by those who regularly take part in sport, the terms are not as familiar to nonathletic participants and the importance of the PI being available to explain was imperative to completion of the questionnaire. As only subjects for whom English was their first language were included in the study no other communication issues were found when administering the questionnaire.

7.9.2 Analysis of Pain and Function using the VISA-A Questionnaire

Despite the limitations noted in section 7.9.1, it would seem appropriate to use the VISA-A questionnaire in any future RCT. This would allow results to be compared with the existing research literature. Taking cognisance of the previously highlighted limitations it would seem appropriate to provide some support to subjects when they complete the questionnaire for the first time. Therefore, the availability of a researcher to provide clarity pertaining to questions or be able to demonstrate single heel raises or single leg hops at the first appointment might help reduce misinterpretation of the questions or failure to complete some questions in the questionnaire.

To establish the effectiveness of the treatment intervention on pain and function in this study the VISA-A questionnaire was administered to subjects at baseline and again at 12 weeks. Twelve weeks corresponded to the end of the eccentric loading exercise plan. The VISA-A scores were analysed within each group and between groups. This allowed both the control and treatment interventions to be evaluated separately regarding their effectiveness as well as comparing the two groups. The analysis of the data was first performed on all subjects including those with missing data. This is referred to as the Intention-To-Treat (ITT) concept and provides a possible solution to two major complications with RCT's which are nonadherence and missing outcomes (Gupta 2011). According to Fisher et al., (1990) ITT analysis includes all randomised subjects in the groups to which they were assigned regardless of their adherence to the treatment protocol, or the treatment they actually received. It also includes subjects who withdraw or are lost to follow-up. The pros of this approach are that it reflects practical clinical scenarios as it admits non-compliance withdrawals and subjects lost to follow-up in a trial. It also fulfils the requirements as detailed in the CONSORT guidelines

on the reporting of RCTs which states that trial data should include deviations from random allocation and missing responses which are considered essential aspects of any trial. However, the cons of this approach are that treatment effect can be conservative due to non-compliance or missing data. To establish whether the missing data influenced the treatment effect in this study, analysis of the data was reppeated on the complete-case data after removing subjects who withdrew or were lost to follow-up and is discussed below.

7.9.3 Treatment effect using VISA-A scores

The mean baseline VISA-A scores were similar in the control and treatment groups. Both groups lost subjects to follow-up with some explanation for this attrition discussed in section 7.3.4. Each group showed an increase in the mean VISA- A score with the control group mean score increasing by 14.42 points from a baseline score of 49.58 ± 17.06 whilst the treatment group increased by 12.73 from a baseline score of 48.07 ± 19.78. When the VISA-A mean score was considered for the complete case data the control group (n=11) score increased by 21.18 from a baseline score of 44.91 ± 5.10 and in the treatment group (n=10) by 12.3 points from a baseline score of 48.50 ± 22.16..In reviewing these results it is important to note that the analysis of data in this study was primarily to trial the methods that might be used in a future RCT and that any results should be viewed with caution as a result of the purposefully small sample size.

A systematic review conducted by Inversen et al., (2012) reviewed studies that utilised the VISA- A questionnaire. They reported that in a review of 18 interventional studies the baseline mean VISA-A score ranged from 24 (Gaweda et al., 2010) to 63 (Knobloch et al., 2010) whilst the post intervention mean scores ranged from 50 (Sayana et al., 2006) to 96.6 (McAleenan et al., 2010), although caution should be exercised when reviewing the results from the study by McAleenan et al., (2010), which considered the effect of a night splint on non-insertional Achilles tendinopathy, in a sample of only five subjects. . Sayana and Maffulli (2007) reported an 11-point increase in the VISA-A scores when used to evaluate eccentric loading exercises in a non-athletic sample, which was similar to the increases in VISA- A scores reported in this study.

Statistical analysis of the VISA-A scores using a Wilcoxon Signed Rank Test was performed on the data as a way of testing the methods to be used in a future RCT. Although, it is envisaged that a future RCT would be suitably powered and where the data was normally distributed analysed using parametric testing. The analysis in this study showed a significantly

significant difference in the VISA-A scores when measured at baseline and at 12 weeks in both control and treatment groups. The analysis was carried out on all subjects including those with missing data and then repeated for the complete data set. Using a level of significance of ≤ 0.05 the control group recorded 0.017 (including subjects with missing data) compared with 0.016 (complete case analysis). In the treatment group the significance level was the same at ≤ 0.012 when including subjects with missing data and for the complete case analysis. In addition, a Mann-Whitney U test failed to show a significant difference in the VISA- A scores between the control and treatment group at baseline and at 12 weeks when including subjects with data missing and for the complete data set.

In addition to proving statistical significance, further analysis of the data also showed a clinically significant improvement in the VISA-A scores when subjects in this study received either the control or treatment interventions. This suggests that both the eccentric loading exercise programme and HVUGI are effective in reducing pain and improving function although caution should be exercised in the interpretation of these results due to the small sample size and the underpowered nature of this study. Although the analysis in this study failed to find a significant difference between the control and treatment groups, a treatment intervention which produces similar improvements as eccentric loading exercises could be a welcome adjunct to treatment options particularly those whose may find the exercises difficult to perform.

7.9.4 HVUGI – evaluation using the VISA-A questionnaire

As previously discussed, the VISA-A questionnaire was administered at baseline and at 12 weeks. The decision to evaluate subjects in the study at 12 weeks reflected the duration of the eccentric loading exercise programme and was considered the smallest period in which subjects could be evaluated post intervention. The review of the literature pertaining to the effectiveness of HVUGI was discussed in detail in chapter 4. It identified seven studies that were carried between 2008 and 2020 which reported reduced pain and improved function following the administration of a HVUGI. Of those seven studies six adopted a case series approach and one a RCT. All the studies that adopted a case series approach except for Wheeler (2014), administered a combined injection of saline, local anaesthetic and a corticosteroid (Chan et al., 2008, Humphrey et al., 2009, Resteghini and Yeoh 2012, Maffulli et al., 2013 and Gronbech –Nielson et al., 2020). In addition, the period of follow-up evaluation varied considerably between studies. Therefore, any comparisons drawn between

the published literature and this study should be viewed in the context of variations in length of follow up and the concomitant effect associated with the addition of corticosteroid.

The study conducted by Resteghini and Yeoh (2012) administered the VISA-A questionnaire at the same time interval as in this study (baseline and at 12 weeks) and reported a mean increase of 28.7 points. This was considerably higher than this study which reported a mean increase of only 12.7 points when including subjects with missing data and 12.3 points for the complete data set.

The study by Wheeler (2014) evaluated the effect of a HVUGI of injectable saline and local anaesthetic (similar to this study) thus aiming to remove any possible effect from the addition of a corticosteroid. The study found an average increase in the VISA-A score of 41 points at a mean duration of follow-up of 347 days. This was considerably higher than this study, which reported an increase of only an average of 12.7 points when including subjects with missing data and 12.3 for the complete data set. The differences reported in the results could be a result of the variation in the time interval for follow-up and the possibility that this could be the result of continued improvement beyond the 12 weeks.

Boesen et al., (2019) also evaluated the effect of the treatment intervention at 12 weeks in their RCT which compared HVUGI administered with and without the addition of corticosteroid. The study found an improvement in pain and function illustrated by an increase in the mean VISA-A score for both groups. The increase in the VISA –A score was greater in the group where corticosteroid had been added to the HVUGI. At 12weeks post-injection the HVUGI group (plus corticosteroid) showed an average increase of 31.9 ± 4.5 points compared with 14.8 ± 3.1 in the non-steroid group. The increase recorded in the non- steroid group is comparable with this study where the average increase was similar.

Boesen et al., (2019) also administered the VISA-A at 6 weeks and found an improvement at this time interval in both groups with the greatest improvement illustrated by an increase in the VISA-A score in those who received a HVUGI with the addition of corticosteroid. However, at 24 weeks the effect of the corticosteroid reduced to a level where no difference was recorded between the two groups. This suggests that the addition of steroid only offers short term improvement which is not maintained. Although some short-term benefits appear to be associated with the addition of corticosteroid to the HVUGI and could result in an earlier return to activity, the increased risk of tendon rupture, subcutaneous atrophy and skin depigmentation associated with corticosteroid would suggest that the risks outweigh these

short-term benefits (Maffulli et al., 2004). However, it is important to note the improvement at 6 weeks in both groups and the importance of earlier evaluation in any future study.

7.9.5 Eccentric loading exercise programme– evaluation using the VISA-A questionnaire.

In this study the control group performed an eccentric exercise programme as described by Alfredson et al., (1998) which consisted of 12 weeks of eccentric exercises which were performed twice daily. A review of the literature pertaining to the effectiveness of eccentric loading exercise programmes in chapter 4 identified several studies which have utilised the VISA-A questionnaire to evaluate the effectiveness of the intervention on pain and function. The study by Sayana and Maffuli (2007) reported an increase in the average VISA- A score in a non-athletic sample (n=34) from 39 ± 22.8 to 50 ± 26.5 (average 11-point increase). Of the 34 subjects in the study, 19 (56%) responded to the exercise programme and needed no further follow up. Of the rest 15 (44%) failed to respond to treatment, of which seven required surgical intervention. In a similar study, but in athletic patients, Maffulli et al. (2008) reported the average VISA-A score increased from an average of $36 \pm$ 23.8 to 52 ± 27.5 (average 16point increase). From a sample of 45 subjects, 27 (60%) responded to the eccentric loading exercises and required no further follow-up. The 18 (40%) who did not improve with the exercise plan were offered an aprotinin injection of which five improved whilst the rest were referred for surgical consideration. These increases in VISA- A scores noted in the Sayana and Maffulli (2007) and Maffulli et al., (2008) were similar to the increases reported in this study with an increase of 14.42 points when including subjects with missing data and 12.3 points when subjects with missing data were excluded from the analysis. However, it is important to note that in the Sayana and Mafulli (2006) study an average increase in the VISAA scores was reported for the whole sample with a mean increase in points greater than that reported as a MCID (McCormack et al., 2015) but 44% of the sample (15 of the 34 patients) did not improve with eccentric loading exercises and were referred for further treatment. Maffulli et al (2008) reported failure to improve in 40% of the sample (18 of the sample of 45) following an eccentric loading exercise programme and required further treatment intervention. In this study of the 18 randomised to the eccentric loading exercise programme 5 were lost to follow-up. Of the 13 who completed the exercise programme 4 (30%) were referred back to the department of orthopaedics for further treatment.

In addition to analysing the pre- and post-intervention effect in the control and treatment group a Mann-Whitney U test was performed to analyse if there was a significant difference between the two groups. Using a level of significance of ≤ 0.05 the VISA –A scores pre and post intervention were compared with no statistical difference reported when comparing the groups with data missing as well as when excluding subjects with incomplete data (Complete case analysis).

What we were unable to establish from this study is if those improvements in the VISA-A score occur earlier in either group as 12 weeks was considered the appropriate time interval, as it enabled the eccentric loading exercise programme to be completed by the control group. A review at 6 weeks in a future RCT would help establish if there are earlier improvements in the treatment group which may be a useful option in clinical practice as it might allow earlier return to activity and reduce the period of immobility. This benefit would need to be traded off against the additional time and effort for participants and the research team in measuring at both 6 and 12 weeks though

7.10 Physiological Measurements

7.10.1 The measurement of Achilles tendon thickness in this study.

One of the key diagnostic features of non-insertional Achilles tendinopathy is evidence of thickening about 2-6cm from the insertion of the tendon into the calcaneus. The tendon either side of this thickened portion has a normal appearance on ultrasound examination, and it is the thickened portion that is referred to when studies on non-insertional Achilles tendinopathy report tendon thickness. The thickening of the tendon is a result of the increased synthesis of proteoglycans and their increased water content which cause changes in the extracellular matrix (Cook and Purdam 2009). As these changes occur in the extracellular matrix the integrity of the collagen fibres is maintained. According to Sharma and Maffulli (2006) ultrasound imaging of non-insertional Achilles tendinopathy shows a disorganised area of collagen fibres with a thickened and hypoechoic area. In addition to showing the structural changes associated with the tendinopathy ultrasound imaging of the tendon allows the tendon thickness to be measured using the diagnostic ultrasound machines integrated measurement tool. The facility to measure the tendon provides a quantitative analysis of the tendon in addition to the qualitative evaluation of the tendon structure.

In this study the same consultant carried out all measurements of tendon thickness at baseline and again at 12 weeks.   No intra-tester reliability testing was performed prior to beginning data collection and may be considered a weakness in this study. As the study was not funded only one consultant radiologist took part in the study and as a consequence blinding to which arm of the trial the subjects were randomised was not possible. A future RCT may require the introduction of an additional consultant radiologist to accommodate the target sample size. If this was a requirement of a future trial, then inter-rater reliability would need to be indexed along with intra-rater reliability prior to the commencement of any physiological measurement including Achilles tendon thickness. This would ideally be performed prior to data collection to ensure the validity and reliability of the data to be collected.

The possible introduction of a second consultant radiologist would also allow blinding to occur assuming both radiologists were available at the same site at the same time but using or having available different clinical spaces. One would be able to measure the tendon thickness and neovascularity and the other would administer the HVUGI in those randomised to that arm of the study. Recruiting two consultant radiologists would be challenging considering the current shortages, so consideration of an Allied Health Professional trained in diagnostic ultrasound could be an alternative option. In addition, if the future, RCT involved a multicentre design then careful consideration would be needed to ensure the availability of researchers/ clinicians and equipment to scan the Achilles tendon and administer the HVUGI.

With regards to the measurement of tendon thickness consideration of variation between different ultrasound machines would also need to be considered if scaling up in a future study resulted in the use of more than one Doppler ultrasound machine. In Chapter 4 the inter and intra-rater reliability of measuring the tendon thickness was reviewed. The study by Dudley-Javoroski et al., (2010) showed high intra tester reliability in experienced operators when compared to the more novice operator whilst McAuliffe et al., (2017) found inter-tester reliability to be between 0.65 and 0.84 (maximum=1). The experience of the operator may well influence the reliability of any measurements taken and should therefore be a consideration when considering the formation of the research team in a future study.

It is also important to consider that with continuing development of ultrasound technology that the ultrasound machines used in a future study may well be an upgraded version of the GE logiq E9 used in this study. Therefore, validity and reliability of any new technology should be established prior to the commencement of data collection.

In this feasibility study the tendon thickness was measured at baseline and at 12 weeks and analysed for all subjects and then again when subjects with missing data were excluded (complete case analysis). With all subjects included the mean tendon thickness reduced from 10.41mm ± 2.8mm to 9.69mm ± 7.23mm in the control group whilst in the treatment group tendon thickness reduced from 11.00mm ± 2.00mm to 10.50mm ± 2.12mm. This is in comparison to a to a similar reduction in the mean tendon thickness in the control group for the complete case analysis from 11.00mm ± 0.87mm to 10.27mm ± 2.47mm. However, in the complete case analysis of the treatment group there was a small, reported increase in mean thickness from 10.40mm ± to 10.50mm ± 2.12mm although the median shows a reduction from 11.00mm (IQR 3) to 10.00mm. While the reported means show some minor changes, clinically the tendons at 12 weeks still appeared thickened in the mid-portion area compared to the proximal and distal portions and was difficult to see during physical examination. Statistical analysis of the mean values using a Wilcoxon Signed Rank Test showed there was no statistically significant change in the tendon thickness because of the HVUGI (treatment group) or the eccentric loading exercise plan (control group) when measured at 12 weeks when including subjects with missing data and when those subjects were excluded (complete case analysis). In addition, using a level of significance of ≤ 0.05 a Mann-Whitney U Test showed no statistical difference in the tendon thickness between the control group and the trial group at both baseline and at 12 weeks when including all subjects and for the complete case analysis. The analysis of the data pertaining to tendon thickness in this study showed only minor changes over the 12-week period which were neither statistically nor clinically significant. It does not appear to correlate with improvement in symptoms noted by the increase in the VISA–A score. However, again we must acknowledge the small sample size used in this study.

Several studies have reported on the effect of treatment intervention on tendon thickness. Maffulli et al., (2013) measured tendon thickness in their study which evaluated the effect of administering a HVUGI for the treatment of non-insertional Achilles tendinopathy. The study, which adopted a case series approach, included 94 athletes. The composition of the HVUGI administered consisted of injectable saline, bupivacaine (local anaesthetic) and Aprotinin. According to Maffulli et al., (2010) Aprotinin a metalloproteinase inhibitor, has been used off label for the management of tendinopathy since the early 2000's. However, there is no evidence in the current literature that it continues to be used. If no improvement was noted at two weeks, then the patient was offered a further HVUGI with the Aprotinin substituted with

corticosteroid. Tendon thickness was measured at baseline and at, 12 months. However, only 59 subjects were available at follow up. In addition, measurements were taken in the subset of subjects who received the second injection. The mean tendon thickness reduced from a mean of 9.1mm ±2.1 at baseline to 7.3mm ± 1.8mm at 12 months. In the subset of subjects who received a second injection at an average follow up time of 3.5 weeks (± 2.1 weeks) the mean tendon thickness was reported to be 8.3mm ± 2.4mm which the authors considered a significant reduction.

The inclusion of only half the sample in the final analysis which included subjects irrespective of whether they received one or two injections, could have influenced the statistical analysis pertaining to tendon thickness. In addition, it is uncertain what short-term effects Aprotinin had on the physiological characteristics of the tendon. However, what is evident is that 45 (48%) of the patients in this study failed to experience sufficient reduction in pain and improvement in function in this subset of patients and required a further injection whilst showing significant reduction in the mean tendon thickness. Therefore, the methodological approach which included the addition of different drugs', the different follow up times and a case series approach on an athletic population makes comparison with this study difficult.

Humphrey et al., (2009) also reported a significant reduction in tendon thickness at 3-weeks post HVUGI. However, caution must be exercised when considering these results as Humphrey et al.'s (2009) study had a sample size of only 11 athletes and included corticosteroid in the injection mixture which could have been responsible for the early reported reduction in tendon thickness.

Resteghini and Yeoh (2012) recorded a statistically significant reduction in mean tendon thickness at 3 months in a case series of 32 patients who received a HVUGI for non-insertional Achilles tendinopathy. It is interesting to note that the maximum tendon thickness reduced from 8.3mm to 7.6mm at 3 months post injection which would be difficult to note through clinical observation. They also measured the thickness of the tendon on the asymptomatic side and found a significant difference between the symptomatic and asymptomatic sides at baseline (pre-intervention). It is important to recognise that the statistically significant reduction in mean tendon thickness on the symptomatic side following the HVUGI was still significantly thicker than the mean tendon thickness reported on the asymptomatic side (7.6mm compared with 5.9mm)

Both the study by Humphrey et al., (2009) and Resteghini and Yeoh (2012) included corticosteroid in the HVUGI which may have had a short-term effect on tendon thickness. Boesen et al., (2019) conducted a RCT trial to compared HVUGI with the addition of steroids with HVUGI without the addition of corticosteroid. The study which had a relatively small sample of 28 (14 randomised into each group) identified that the mean reduction in thickness was greater in the group who received a HVUGI which contained corticosteroid than in the group which did not contain corticosteroid. This difference was recorded at 6 and 12 weeks with very little difference between the groups reported at 24 weeks. As the sample size is relatively small caution should be exercised with regards to the results however it does suggest that the addition of corticosteroid could result in greater reduction in tendon thickness over the short-term, but the increased effect reduces over the longer period. If the results of Boesen et al., (2019) study are compared with this study then the reduction in mean tendon thickness at 12 weeks is comparable. They reported a reduction in the mean tendon thickness at 12 weeks post injection without the addition of corticosteroid of 0.7mm compared with this study which was 0.5mm.

Although we can show comparable results to the studies above, what is evident is that the reduction in tendon thickness in this feasibility study is neither statistically nor clinically significant. The tendon still appears thickened in comparison to the normal tendon thickness post-intervention. The reduction in thickness has no relationship to the reduction in pain and improved function as determined by the VISA-A scores. Therefore, the benefit of measuring the tendon thickness in any future RCT is questionable and may not have any bearing on the functional outcome which is more important than any physiological measure.

Due to this uncertainty pertaining to tendon thickness and taking cognisance to the small sample in this study further consideration regarding its inclusion in any future study will be discussed in the recommendations section 7.15.

7.10.2 Measurement of neovascularity in this study

Neurovascular ingrowths, alongside thickening of the Achilles tendon and alterations to the matrix, are key diagnostic features of non-insertional Achilles tendinopathy. Leung and Griffiths (2008) described a correlation between neovascularisation, tendon thickening and focal hypoechoic areas in symptomatic tendons. This has resulted in the measurement of neovascularity becoming common place in studies where Doppler ultrasound is available. The theory is that any intervention which results in a reduction in pain and improvement in function should correlate

with a reduction in the neovascularity. This need to evaluate neovascularity resulted in the development of a modified scoring system first described by Ohberg et al. (2001). This semi-quantitative grading system, previously discussed in Chapter 4, has been shown to have excellent intra- and inter-rater reliability (Sengkerij et al.,2009). However, the results pertaining to the existence of neovascularity in symptomatic tendons are conflicting and vary considerably.

In our study 90% of subjects (n=28) exhibited evidence of neovascularity when examined at baseline. This compares with 66% of tendons exhibiting neovascularity in the study by Watson et al., (2017), whilst the study by Zanetti et al., (2003) found evidence of neovascularity in 30 of 55 symptomatic tendons (55%) but only in one of 25 asymptomatic (4%) tendons. These are contrary to the results from a study by Ohberg and Alfredson (2004) who found that all patients in their study (41 tendons in 30 patients) exhibited neovascularity when examined with Doppler ultrasound. Following a 12-week eccentric loading exercise plan and at a mean follow-up of 28 months, 36 of the 40 tendons (90%) were asymptomatic with no pain reported during activity. Of those 36 tendons, 32 did not show any signs of neovascularity (89%). This contrasts with this study which found no relationship between neovascularity and the VISA-A score with the mean neovascularity score reduced but with 21 of the 23 tendons examined at 12 weeks still exhibiting neovascularity. However, it should be noted that the mean follow-up is significantly longer in the study by Ohberg and Alfredson (2004), than the 12-week post intervention follow-up in this study and therefore the rehabilitation process would be more complete.

De Jonge et al (2013) explored the relationship between the VISA–A score and neovascularity in a study of 127 patients (140 tendons). This cross-sectional study analysed data from three clinical trials including two RCTs and one prospective clinical trial. All the studies included eccentric loading exercises. Two of the RCTs included additional therapies of night splints and platelet rich plasma injections. The authors analysed the VISA-A results as three different domains which included pain, function and activity. Although the original design of the questionnaire allowed for this, almost all studies only consider the overall VISA–A score and do not consider the separate domains. In this study there was no significant relationship between the pain and activity domains and neovascularity, but there was a relationship between neovascularity and function with a lower mean VISA-A score in those tendons with evidence of neovessels. However, the regression coefficient showed a weak relationship. The fact that this study failed to find a relationship (on an underpowered sample) between

neovascularity, and pain challenges the previous held belief that pain is a result of the ingrowth of neovessels (Alfredson et al., 2003).

The failure in this feasibility study and in other studies to identify a relationship between neovascularity and the VISA-A might question the value of this physiological measurement in any future RCT. However, variation in the published literature may be a result of the time intervals that measurements were performed. Although the use of an ultrasound scan is useful pre-intervention, and an obvious necessity for administering the HVUGI, the omission postintervention would reduce the need for the services of a suitably qualified sonographer, thereby reducing project costs and increasing appointment capacity at more than one site. However, with such varied results the inclusion in a future RCT should be further investigated and is discussed in the recommendations detailed in chapter 7.15.

7.11 Summary of feasibility study findings

The process of data collection performed in this study was as expected in a future RCT. Although the data in many cases was normally distributed caution was exercised as the sample size was small and as such nonparametric analysis was performed. The expectation is a future RCT would be appropriately powered, and where data is normally distributed parametric analysis performed. In addition, hypothesis testing would be performed as part of the overall data analysis.

With regards to the findings of this study the feasibility of carrying out a future RCT could be challenged by issues surrounding recruitment, retention, and adherence to the eccentric loading exercise plan. On reviewing the current literature and reflecting on the methodological approach in this study highlighted our failure to evaluate if the administration of a HVUGI results in earlier improvement compared with an eccentric loading exercise plan. Therefore the recommendation from this feasibility study is that a follow-on pilot study is conducted. Dependant on the findings of the pilot study the proposed hypothesis for a future RCT would be as follows in section 7.15. It is also important to acknowledge that the secondary aims in this study would form the primary aims of any future RCT.

7.12 Limitations /findings of the study

This study attracted no external funding which resulted in limited access to both the human and material resources required to carry out the study. Initially one session per week was ringfenced to carry out this study. This ring fencing included the use of clinical space, an

ultrasound scanner and the services of a Consultant Radiologist. With a sample size of 30 it was anticipated that the recruitment would take four months. However, due to some reorganisation of clinics within the department of Radiology and the reduced availability of the consultant radiologist to just one hour per week between 8am and 9am the recruitment time required to be extended. The reduced availability part way through the study created a lag between screening and enrolment which caused some concern amongst those patients who volunteered to participate in the study. The revised early morning scheduling was a problem for a number of patients which resulted in some of those eligible declining to participate. The alteration occurring part way through meant that some participants recruited early in the study were lost to follow-up. This resulted in a reported attrition rate of 26% which would need to be addressed and reduced to below the desired level of 20% in any future study (Schulz and Grimes 2002).

This feasibility study has shown that it is feasible to measure VISA-A scores 12-weeks postintervention. However, there was no statistically significant difference in VISA-A scores between the intervention and control groups when reviewed at 12-weeks. The decision to carry out post-intervention follow-up at 12 weeks means that any earlier gains in the treatment group compared to the control group could not be ascertained. This would be important to establish as improvement occurring earlier in the treatment group might allow early mobilisation and return to activity. It would also be useful to establish if the improvements are sustained and as such follow-up at 6 and 12 months might also be beneficial.

The subjects randomised to the control group were expected to perform potentially painful exercises twice daily for 12 weeks. Adherence was recorded with the use of a self-reported diary. The measured adherence was calculated at 74%, just short of the 75% target used by other authors (Sayana and Maffuli 2007).

7.13 Recommendations

In reviewing the findings of this study, several areas have been identified that require further investigation and monitoring to ensure that both the researcher and any prospective funders are confident that a future RCT could be conducted safely and effectively whilst ensuring sufficient numbers could be recruited and retained for the duration of the study.

The areas requiring further investigation are highlighted below along with some revisions to the methodological approach which will be re-evaluated prior to inclusion in a future RCT.

The intention is to re-evaluate the proposed changes by carrying out a pilot study prior to applying for funding. The title of the study would be:

Treating Achilles tendon pain – A pilot randomised trial to compare the use of saline injections verses exercises. (See link below) https://qmumy.sharepoint.com/:w:/g/personal/jveto_qmu_ac_uk/EQCtm56h8uFDkLWXqYA8WgcBY8g56R6n2jMUWp_TtwDuPA?e=sPwYcw

The study would be a small scale, pilot version of a proposed future RCT and would aim to recruit and randomise patients into a control group (ELE programme) or a treatment group (HVUGI). The pilot study would build on the feasibility work carried out as part of this study and would focus on some key areas that have been highlighted as areas of concerns regarding any upscaling to a suitable powered RCT.

If these proposed changes incorporated into the pilot study design are found to be effective, they would be included in the design of a future RCT. If on the contrary the changes fail to address the issues highlighted in this study, then further changes could be considered prior to any funding application being considered or support the decision not to proceed with any future study.

Proposed hypotheses for a future RCT.

There is a significant increase in the VISA-A score and significant reductions in the thickness of the Achilles tendon and Öhberg's neovascularity score with the administration of a HighVolume Ultrasound Guided Injection compared to eccentric loading exercises in patients with non-insertional Achilles tendinopathy.

7.14

Areas requiring further investigation in the proposed pilot study.

7.14.1 Recruitment/ retention

The lack of funding in this study reduced the capacity to use more than one site and limited the availability of appointments, which affected recruitment and retention. The addition of another site in a future RCT would provide more convenience to subjects by reducing travel distance and increasing the availability of appointments. However, increasing the numbers of sites to two would require more staff resources as well as access to additional clinical space and equipment. This would increase the economic costs of the study which is an important consideration for potential funders. Where more than one clinician is involved in data collection or the administration of an intervention then it is important that protocols are clearly established, and that inter- and intra-rater reliability is considered prior to starting the study. These are all important considerations. However, the challenge might be the recruitment of an additional consultant radiologist into the study. According to the Royal College of Radiologists (2019) one in four hospitals in the UK do not have enough radiologists to keep patients safe and is resulting in outsourcing of services to the private sector. Therefore, increasing the availability and resources in one site might help reduce costs and reduce the number of researchers /clinicians involved in the study whilst maintaining the recruitment rate and retention. Another option would be to employ a suitably qualified Allied Health Professional (AHP) who is able to perform ultrasound and administer the HVUGI. Consideration regarding their level of experience would need to be considered. This would have the potential to reduce costs in any future RCT and address the challenge surrounding the shortage of consultant radiologists.

The pilot study would aim to recruit subjects via one site but provide scheduling which included both morning and afternoon appointments (2 x 3-hour sessions). The effect of the revised appointment scheduling on recruitment and retention would be evaluated. The recruitment and retention in the pilot study would be monitored against the levels previously reported in chapter 7 figure 7.1. Recruitment rate target would be to recruit 30 subjects (see section 5.6) at a rate of 2.6 patients per week (overall 12-week recruitment period). The retention threshold would be 80% of those recruited completing the study.

7.14.2 Adherence to the ELE programme

Adherence to the ELE programme in this study fell short of the 75% adherence rate previously reported as the minimum requirement by Roos et al., (2004) and the threshold used in the study conducted by Sayana and Maffulli (2006). In this study adherence was recorded at 74% based on the adherence diaries returned at the 12-week review appointment. This failure to reach the 75% threshold were discussed previously and some proposals suggested that would hopefully increase the adherence rate to above the agreed threshold. These proposals are detailed below and will be incorporated into a pilot study. The impact of these changes to the current methodology will be assessed as part of the pilot study and incorporated into a future RCT if deemed effective.

The plan would be to continue the use of adherence diaries which will be completed by the subjects daily and will help the researchers determine the number of sessions completed along with the number of sets and repetitions of each exercise in the programme. In addition, text messaging would be incorporated into the pilot study with subjects receiving an SMS text message at 2-week intervals to encourage participants to carry out the exercises as prescribed. The plan to administer the VISA-A questionnaire at 6 weeks, which corresponds with the halfway point of the ELE programme, will also serve as a reminder to complete the exercises.

7.14.3 Early evaluation of pain and function (VISA-A questionnaire)

As previously discussed in this feasibility study the VISA-A questionnaire was administered at baseline (pre-intervention) and at 12 weeks which corresponded with the completion of the ELE programme. Therefore, we were unable to establish if the improvements in function and reduction in pain seen at 12 weeks occurred earlier in the treatment group, therefore the intention in the pilot study is to administer the VISA-A at baseline, 6 weeks and at 12 weeks. This will help establish if early improvements vary between the treatment and control group. As the VISA-A questionnaire is self-administered the intention would be to post the questionnaire to all subjects at 6 weeks and review subjects in person at baseline and 12 weeks. The plan to review participants in person at baseline would help with any comprehension issues they may have with the content of the questionnaire.

7.14
.4 Relationship between VISA-A, tendon thickness and Neovascularity

Earlier in the chapter it was reported that no relationship between tendon thickness, neovascularity and the VISA-A score was found in this study. A review of the literature was inconclusive with some authors identifying the relationship while others did not. Therefore, this area needs further careful evaluation to consider the value of including these objective measures in a future RCT.

The intention in the pilot study would be to measure tendon thickness, and neovascularity in all subjects at baseline and at 12 weeks. The data will be analysed using a correlation coefficient (Pearson's r). This will measure the strength and direction of the relationship between the VISA-A score and tendon thickness and the VISA-A scores and the neovascularity score for both the control group (ELE programme) and the treatment group (HVUGI).

The expectation is that there would be a negative correlation coefficient reflecting that improved function and reduced pain (Increased VISA-A score) would be associated with a reduction in tendon thickness and a reduction in the neovascularity score.

In the pilot study if there is a correlation coefficient of -0.6 or above then it would be considered a moderate to strong negative relationship between the VISA-A scores and tendon thickness and neovascularity scores (Taylor 1990). The findings of the pilot study would be considered when deciding if these objective measures are included in a future RCT.

The decision to include the measurement of tendon thickness and neovascularity will also have an impact on the workload of the consultant radiologist who would not be required to carry out this measurement and would only be employed to administer the HVUGI in those subjects randomised to the treatment group. It would also reduce the facilities and equipment needed to support any future study. Therefore, it is important that the correlation between these objective measures is investigated and used to help guide the methodological approach in a future RCT.

7.14.5 Economical evaluation
The MRC guidance on complex interventions published in 2006 (Craig et al., 2006) were used to help develop this feasibility study. However, it is important to acknowledge that a revised

7.14

framework jointly commissioned by the MRC and the National Institute of Health Research

was published in 2021 (Skivington et al., 2021) This new framework in addition to evaluating

the effectiveness of an intervention also highlights the importance of whether an intervention is implementable, acceptable, and cost effective.

Therefore, as part of the proposed pilot study an economic evaluation will be carried out, to assess the cost effectiveness of administering a HVUGI compared to an eccentric loading exercise programme. As NHS resources are limited it is important to establish if any intervention represents good value for money. In order to perform an economic evaluation both costs and outcomes must be analysed, and more than one alternative strategy must be compared (Goodacre and McCabe 2002). If the outcomes of both the treatment and the control intervention are found to be similar, then a cost minimisation analysis could be carried out. This simply compares the cost in determining which intervention to choose with most providers deciding on the cheapest option. Where outcomes are not equivalent a cost effectiveness analysis could be considered. This method of analysis considers both the cost of the intervention and the effectiveness of the treatment and presents the results as a cost-effectiveness ratio. Although it is right and proper that an economic evaluation is performed as part of any implementation process, it should not be the single determinant in deciding the choice of intervention. This should be based on the individual needs of the patient.

7.14.6 Non-inferiority and equivalence trials

This feasibility study and proposed pilot study were designed to assess the feasibility of carrying out a future RCT. As is common with this type of study the design was based on a planned superiority trial which aimed to show that the administration of a HVUGI is superior to an eccentric loading exercise programme However, it is important to recognise that sometimes establishing that a new treatment is equivalent or not inferior to the current treatment can be useful where patients present with co-morbidities, which prevent the use of the standard treatment. However, according to Chan et al., (2004) the finding of equivalence or non-inferiority trials may be a result of a small sample size, failure to randomise participants, lack of blinding and the effects of concomitant therapies. Therefore it is recommended that the same rigour is adopted as in superiority trials, whilst recognising that the sample size calculations will vary between the different types of trial. In equivalence trials the aim is to establish if the clinical effect of the two treatment interventions is identical. However, from a practical perspective equivalence is determined if the effect between two treatments lie within a specified interval which is plus or minus the level of clinical significance. On the contrary a non-inferiority trial would consider a new treatment was non

inferior if the difference in effect between the new treatment and the control treatment was less than minus the level of clinical significance (Christensen 2007). Although the superiority trial is the most commonly used type of RCT an awareness of other methodological approaches and the subsequent outcomes will be important in the development process for a future RCT. Irrespective of which type of trail is considered in the future the primary and secondary aims in the proposed pilot study are still key in the development process. However, the addition of an economic evaluation may well influence the type of trail adopted in a future trial.

7.14.7 Monitoring for metabolic disease

A review of the literature in chapter 3 identified that some metabolic disorders are associated with the development of non-insertional Achilles tendinopathy which might influence nonsurgical management. Therefore, as part of the screening process subjects will be asked if they have diabetes or hyperlipidaemia. In addition, their BMI will be calculated and recorded. There is no intention to exclude subjects with these metabolic conditions but rather monitor and correlate with the outcome data, to establish if these conditions effect the outcomes from the control and treatment interventions.

7.15 Areas of success identified from this study

The method adopted for recruitment of subjects into this study was successful with the capacity to scale up recruitment to include patients attending clinics in primary care.

The inclusion and exclusion criteria were robust enough and were comparable to the criteria used in other studies. The method adopted for randomising the subjects using the online randomisation system offered by sealed envelope was easy to set up and use and would be used again in the pilot study and in any future trial. The intention would be to continue to use simple block randomisation to ensure similar numbers in both arms of the trial and reduce potential bias. Blocks of 2, 4 and 6 would be utilised in the pilot study.

The method employed for administering the HVUGI described in Chapter 5 and reported by other authors would continue to be used in the pilot study. The information provided and demonstration of the eccentric exercises appeared adequate to allow subjects in the control group to carry out the exercises. However, guidance regarding comprehension of the questions in the VISA-A questionnaire should be provided to improve completion of the questionnaire.

In any future RCT consideration would be given to include subjects where English is not there first language. The VISA-A questionnaire continues to be validated in other languages which would help with its administration. However, it is important that subject give informed consent to participate in a clinical trial and as such careful consideration would be given to the use of translation services to provide written and verbal support where necessary.

8.0 CONCLUSION

The aim of this study was to assess the feasibility of carrying out a future RCT to compare the use of HVUGI with an eccentric loading exercise programme for the treatment of noninsertional Achilles tendinopathy. The primary outcomes measured in this study included eligibility, recruitment, retention and adverse events whilst the secondary outcomes included measuring the effect on pain and function of HVUGI compared with eccentric loading exercises using the VISA-A patient reported outcome measure. The effect of the treatment and control interventions on tendon thickness and neovascularity was also measured.

The study found the feasibility of carrying out a future RCT was possible, but challenges existed with recruitment, retention and adherence to the eccentric loading exercise programme. Therefore, a pilot study with some modifications made to improve these areas of deficit is proposed and should be carried out and evaluated before considering whether to proceed to an RCT.

The study highlighted the need to establish if the HVUGI resulted in early resolution of symptoms compared to the eccentric loading exercises. The VISA-A questionnaire was administered to both the treatment and control group at 12 weeks which corresponded to the completion of the eccentric loading exercise programme. Failure to carry out an earlier evaluation using the VISA-A questionnaire was a significant oversight as early mobilisation and return to activity would be seen as a benefit of using the HVUGI even if at 12 weeks the benefits of both treatments were similar. The economic and health benefits of an early return to physical activity or work could be considerable both to the individual and the Employment and Support Allowance budget. Therefore, the intention would be to include the administration of the VISA-A at 6 and 12 weeks in the proposed pilot study.

Although the results of the secondary outcome measures should be viewed with caution due to the small sample size, an alternative treatment to eccentric loading exercises which provides comparable results regarding reduction in pain and improved function could be considered a valuable adjunct to non-surgical management. However, further research including a pilot study to address the deficits and methodological issues identified in this study is proposed. Dependant on the findings of the pilot study, a possible future RCT could add to the current research evidence that is available pertaining to the use of HVUGI for the treatment of noninsertional Achilles tendinopathy.

8.1 Areas of future research

Whilst the research process adopted in this study highlighted key issues which could challenge the feasibility of carrying out a future RCT it also highlighted gaps in the research literature which limit our current understanding of how HVUGI work,, expectations of the non-athletic population with respect to treatment outcome and aspects of tendon structure and function..

8.1.2 The less physically active population

An extensive search and appraisal of the literature pertaining to the administration of HVUGI in the treatment of non-insertional Achilles tendinopathy was discussed in Chapter 4. It identified that the study populations in the published literature were primarily physically active individuals who regularly participated in sport. This challenged the generalisation of the results to a non -athletic population as commonly seen in the hospital outpatient setting. The expectations of those who actively participate in sport is to return to pre-injury levels of activity. Unfortunately there is no evidence to support the expectations of non-athletic patients following treatment. The focus on return to pre-injury levels of activity are reflected in the VISA-A questionnaire which devotes 40% of the quantitative scoring to questions pertaining to loading of the achilles tendon during sport. Therefore from a quantitative perspective it would seem reasonable to think that an accepted outcome in the non-athletic population could occur at a much lower VISA-A score. Therefore the validity and reliability of the VISA-A questionnaire should be evaluated in a non-sporting population. In addition understanding the lived experience of this patient population might help our understanding of what constitutes a good outcome, help clinicians achieve their patient expectations and facilitate discharge from care.

8.1.3 Tendon structure

In Chapter 2 the structure and function of the Achilles tendon was discussed and the pathological changes associated with non-insertional Achilles tendinopathy discussed in chapter 3. Unfortunately the literature failed to identify any structural differences in the Achilles tendons of those who are physically active and participate in sport and those that are considered non-athletic. We know that cell matrix interactions are dynamic and that connective tissues will not only turnover as part of the homeostatic process but will also remodel in response to different stimuli. According to Screen et al., (2015) the adaptive response can cause the tendon to thicken and strengthen in response to use. What is not well

understood is what levels of loading and activity is optimum for tendon function and adaption. It is known that overloading of the tendon can cause structural changes and damage if the loading results in levels of stress that exceed the yield point on the stress strain curve. Biologically overuse has been reported to initiate a catabolic cell response and tendon degeneration. Therefore future research should focus on identifying if there are structural differences between the Achilles tendon of athletic and non-athletic patients, whilst also trying to establish the optimum loading levels to prevent the structural changes of Achilles tendinopathy, whilst promoting the positive adaptive changes which cause thickening and strengthening of the tendon.

8.1.4 High Volume Ultrasound Guided Injections.

One of the classic features of non-insertional Achilles tendinopathy is evidence of neural ingrowths with neovascularisation. Early studies by Ohberg and Alfredson (2002) showed that sclerosing these neo-vessels was associated with a reduction in pain and improved function. Initially polidocanol was used as a sclerosing agent, but with no licence in the UK researcher adopted the use of HVUGI as an alternative method of reducing the neovessels.

However more recent studies have questioned the link between the reduction in the neovessels and reduction in pain and improved function. Drew et al., (2014) failed to find any positive correlation between reduced neovascularity and Achilles tendon pain. Therefore it is unclear what the mechanism by which, HVUGI works. In addition there is no research literature which reports on how the optimum dose was established (although 40ml is universally accepted). As a consequence future research should try to establish what effect injecting a high volume of saline around the tendon has on the structure of the tendon and the surrounding tissues. In addition a trial to investigate the effect of different volumes of saline injected on pain and function would help establish what the optimum volume should be administered.

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Appendices

Appendix 1

Participant Information Sheet

Participant's information sheet

Treating Achilles tendon pain- A feasibility study of saline injections verses exercises

You are being invited to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Contact us if there is anything that is not clear or if you would like more information. Take time to decide whether you wish to take part.

Why have I been chosen?

You have been invited to take part in this study because you have been referred by your GP with pain in your Achilles tendon particularly when walking or doing other types of exercise. It is also likely that you have noticed swelling in the tendon which is painful when squeezed. The current treatment for this condition is to carry out a 12-week exercise programme. Although in most people these exercises provide good short- and long-term results, they can be burdensome, time consuming, difficult to carry out and painful. There is reason to believe that you might get similar relieve if we inject saline (salty solution) around your painful Achilles tendon. Both treatments are currently used in the department, however we are unsure which one is better. Before carrying out a large-scale study to compare the two treatments we must carry out a feasibility study to ensure that we can recruit enough patients, whether the treatment is acceptable to patients and whether the planned method of carrying out the study works in practice. Although this is a feasibility study it is hoped that the treatment you receive will improve your symptoms. If it does not help your symptoms, you will be offered alternative treatment as any other patient attending the department of orthopaedics and trauma with this problem.

Do I have to take part?

No the decision to take part in the study is entirely yours. If you do decide to take part you will be asked to sign a consent form. Even if you do agree to take part you can withdraw at any

time without affecting your right to care. If you do not wish to take part in the study your treatment will not be affected and you will receive the current treatment which is likely to be the 12 week eccentric loading exercise programme.

What would taking part involve?

If you agree to take part you will be given an appointment to attend the Department of Radiology at the Royal Infirmary Edinburgh. We will carry out an examination followed by an ultrasound scan to check whether you fulfil the criteria to take part. The ultrasound scan will confirm the clinical diagnosis in addition it will allow us to measure the thickness of the Achilles tendon and identify and count any small blood vessels which form around an injured tendon. Diagnostic ultrasound is safe and does not expose you to any dangerous radiation

Once you consent to take part in the study, you will be randomly allocated to one of two groups. The Randomisation is carried out remotely by a computer programme and the principle researcher has no control over which group that you are allocated too. Only when you have commenced the study will you be removed from the general orthopaedic waiting list to ensure that you are not disadvantaged whilst considering taking part. .

Group A

If you are allocated to Group A you will receive an exercise programme which consists of a series of exercises that you perform twice a day for 12 weeks. In addition you will also be asked to complete a Questionnaire which consists of 8 questions. This process including the initial examination and ultrasound scan should take no longer than 45 minutes. You will be supplied with an information sheet illustrating the exercises you are required to carry out and a diary to record how often you actually do them during the 12 weeks. If during the 12 week period you experience any exacerbation of your symptoms then you can contact the principle researcher who will be able to give you advice.

At 12 weeks we will see you back in the Department of Radiology to complete the Questionnaire again and have another ultrasound scan to measure the thickness of the tendon and the number of small blood vessels. This should take no longer than 30 minutes. If at the end of the 12 week period you are still in pain you will be offered normal alternative treatments as any other patient to try and resolve the problem.

Group B

If you are allocated to Group B you will receive an injection of saline (sterile salty water) around your painful Achilles tendon. You will be asked to complete a Questionnaire which consists of 8 questions prior to receiving the injection. The injection will be guided using ultrasound to ensure the correct positioning. In addition to saline the injection will include local anaesthetic which should help reduce any pain during the injection and for a period of about 8 hours after the injection. The process including the initial examination and ultrasound should take no longer than 45 minutes. If you have pain when the anaesthetic wears off you can take what you would normally take for a headache. We would not expect you to have any pain after the first 24 hours however if you do experience pain or have any reaction to the injection, please contact the principle researcher who will be able to give you advice as to what to do.

At 12 weeks we will see you back in the Department of Radiology to complete the questionnaire which you performed at the start of the study. You will also have another ultrasound scan to measure the thickness of the tendon and the number of small blood vessels. This process should take no longer than 30 minutes. If at this stage you are still in pain you will be offered normal alternative treatments as any other patient to try and resolve your problems.

What are the possible benefits to taking part?

Both treatments offered in this study are normally offered in the department. They have both been shown to reduce symptoms in some patients however this cannot be guaranteed. However your participation in this study may help future patients who have Achilles tendon pain.

What are the possible disadvantages and risks to taking part?

Taking part in the study should not disadvantage you in anyway. No known risks have been reported in studies which have injected saline around a painful Achilles tendon. Some people might find the injection unpleasant but the addition of local anaesthetic should reduce any post injection pain. On rare occasions (less than 1%) people have been known to experience an allergic reaction to the local anaesthetic. If you have a known allergy to local anaesthetic you will be excluded from the study. If you experience a reaction during the study we are equipped to deal with your situation which might include the administration of an injection of adrenaline.

In addition if we identify something on the scan such as a tear in your tendon, we will organise any further investigation and treatment you require.

What happens when the study is finished?

At the end of the research study you will be provided with the outcome of the study. If you continue to experience pain in your Achilles tendon we will continue to provide you with care.

Will my taking part in the study be kept confidential?

All the information we collect during the course of the research will be kept confidential and there are strict laws which safeguard your privacy at every stage. Your name will be removed and replaced with an anonymised study number so that you cannot be recognised from it. With your permission we will inform your GP that you are taking part.

Who is organising the research and why?

This is study being carried out as part of a clinical doctorate programme at the University of Stirling. No external funding has been provided for the study.

Who has reviewed the study?

The study has been reviewed by the research ethics committee at the University of Stirling and by NHS South East of Scotland Research Ethics 02.

Contact for Further details

If you have any further questions about the study please contact John Veto on jveto@nhslothian.scot.nhs.uk or by telephone 0131 536 3716
If you would like to discuss this study with someone independent of the study please contact:
Professor Ronan O'Carroll, Director of Research, Division of Psychology on reo1@stir.ac.uk or by telephone 01786-467683

Complaints

If you have a complaint about any aspect of the treatment you receive on this study then you can contact

The Patient Experience Team
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
Telephone Number 0131 536 3370
Email feedback@nhslothian.scot.nhs

Appendix 2

Consent form

UNIVERSITY *of* STIRLING

Consent Form

Study Title

Treating Achilles tendon pain- A feasibility study of saline injections verses exercise

…………………………..

Name of Researcher:

John A Veto

Please initial box

1. **I confirm that I have read the information sheet dated.................... (version............) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.**

2. **I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.**

3. **I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from NHS Lothian. Where it is relevant**

to my taking part in the research I give permission for these individuals to have access to my records

4. **I agree to my General Practitioner being informed of my participation in the study.**

5. **I agree to take part in the above study.**

Name of Participant   **Date**   **Signature**

Name of Person   **Date**   **Signature**

Contact details of the Principle Researcher

Name	**John A Veto**
Address	**Department of Orthopaedics and Trauma**
	Royal Infirmary of Edinburgh
	Lauriston Building
	Edinburgh

Email /telephone John.Veto@nhslothian.scot.nhs.uk 0131 536 3716

Appendix 3 GP letter (template)

UNIVERSITY *of* STIRLING

Mr John Veto

Senior Lecturer in Podiatry

Department of Orthopaedics and

Trauma

Lauriston Buildings

Edinburgh

Dr. …………………..

Practice Name

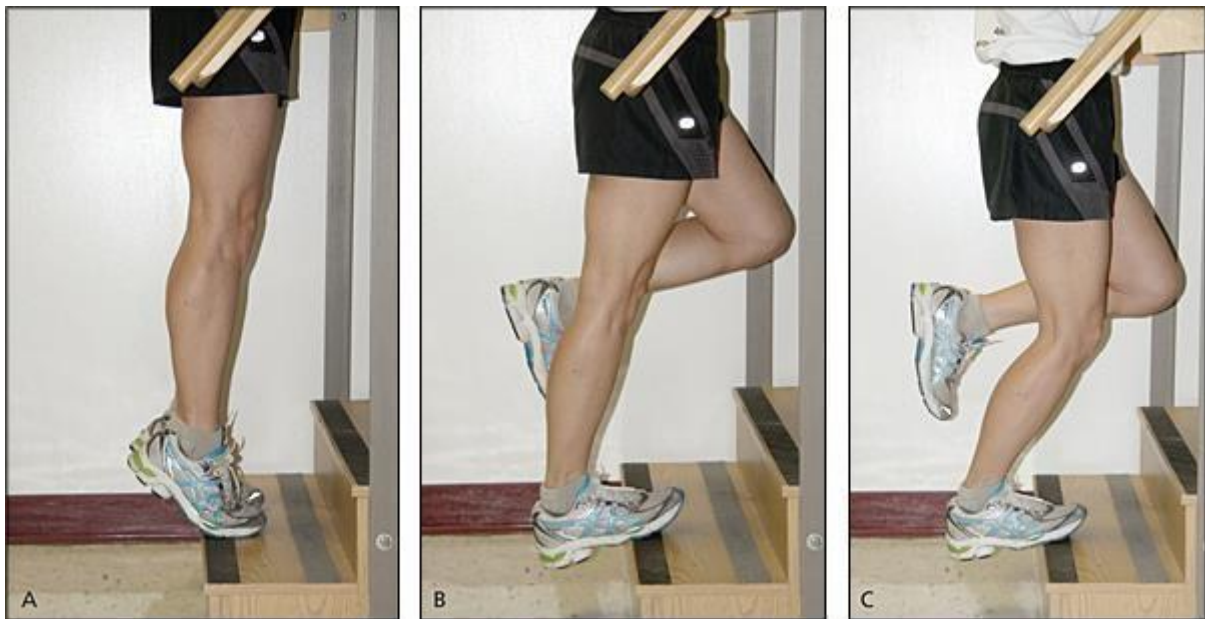Practice Address

Dear Dr.

Patient Name

CHI Number

I write to inform you that the above named patient you referred to the Department of Orthopaedics and Trauma with non-insertional Achilles tendinopathy on the dd/mm/yyyy has consented to participate in a trial evaluating the use of high volume ultrasound guided injections for the treatment of their condition. It is a pilot study to assess the feasibility of carrying out a larger scale RCT. They will be randomized to either receive the high volume injection or the current treatment of a standard eccentric loading programme. If they have showed no improvement at the end of the 3 month trial period alternative treatment options will be offered as in the case of any other referred patient.

If you require any further information about the trial please do not hesitate to contact me via email jveto@qmu.ac.uk or by phone.

Yours Faithfully

John A Veto
Appendix 4

Eccentric loading exercise sheet and guide

Thank you again for agreeing to participate in the research study. As previously advised you have been randomised to the group who will carry out the eccentric loading programme. This programme is the most commonly prescribed for Achilles tendinopathy or Achilles tendonitis as it is sometimes referred.

The programme involves you carrying out exercises A and B twice a day for 12 weeks. You may find when you initially start the exercises that you are not able to complete the required number of repetitions as prescribed. You may also find them painful to perform which is considered normal. You should if possible carry these exercises out on the bottom step of your stairs. You can use the wall and banister to help with balance but try to avoid taking any weight on your arms.

Exercise A (Heel lowering with knee straight)

- Stand on the bottom step with you heels off the step.
- Rise on your tiptoes taking most of the weight on your good leg as you rise (Diagram A)
- Once you are on your tiptoes and with your knee straight transfer the weight to your sore leg by lifting your good leg of the step.
- Slowing lower the heel of your sore leg until it is lower than the step as in in Diagram B.
- Using your good leg again rise on your tiptoes and repeat the exercise.

- **You should do 15 repetitions of exercise A 3 times (total of 45 repetitions) morning and Evening**

- **Record the number of repetitions of each exercise you do each day in the diary provided.**

Exercise B (Heel lowering with knee bent)

- **Stand on the bottom step with you heels off the step.**
- **Rise on your tiptoes taking most of the weight on your good leg as you rise (Diagram A)**
- **Once you are on your tiptoes and with your knee straight transfer the weight to your sore leg by lifting your good leg of the step.**
- **Bend the knee of you sore leg as in Diagram C**
- **Slowing lower the heel of your sore leg until it is lower than the step as in in Diagram B.**
- **Using your good leg again rise on your tiptoes and repeat the exercise.**
- **You should do 15 repetitions of exercise A 3 times (total of 45 repetitions) morning and evening.**

Appendix 5 Eccentric loading exercise diary (extract)

Week 1

Week commencing ……………………….

You should aim to complete 3 sets of 15 repetitions of exercise A. Please record how may you do each session. If you miss doing the exercises for any reason just put 0 against the date.

Exercise A	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Morning							
Evening							

You should aim to complete 3 sets of 15 repetitions of exercise B. Please record how may you do each session

Exercise B	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Morning							
Evening							

Appendix 6   VISA –A questionnaire

IN THIS QUESTIONNAIRE, THE TERM PAIN REFERS SPECIFICALLY TO PAIN IN THE ACHILLES TENDON REGION.

1. For how many minutes do you have stiffness in the Achilles region on first getting up?

100 mins `| | | | | | | | | | |` 0 mins   Points: ☐
0 1 2 3 4 5 6 7 8 9 10

2. Once you are warmed up for the day, do you have pain when stretching the Achilles tendon fully over the edge of a step? (keeping knee straight)

strong severe pain `| | | | | | | | | | |` no pain   Points: ☐
0 1 2 3 4 5 6 7 8 9 10

3. After walking on flat ground for 30 minutes, do you have pain within the next 2 hours?
(If unable to walk on flat ground for 30 minutes because of pain, score 0 for this question).

strong severe pain `| | | | | | | | | | |` no pain   Points: ☐
0 1 2 3 4 5 6 7 8 9 10

4. Do you have pain walking downstairs with a normal gait cycle?

strong severe pain `| | | | | | | | | | |` no pain   Points: ☐
0 1 2 3 4 5 6 7 8 9 10

5. Do you have pain during or immediately after doing 10 (single leg) heel raises from a flat surface?

strong severe pain `| | | | | | | | | | |` no pain   Points: ☐
0 1 2 3 4 5 6 7 8 9 10

6. How many single leg hops can you do without pain?

strong severe pain/unable `| | | | | | | | | | |` no pain   Points: ☐
0 1 2 3 4 5 6 7 8 9 10

7. Are you currently undertaking sports or other physical activity?

0 = Not at all
4 = Modified training ± modified competition
7 = Full training ± competition but not at same level as when symptoms began
10 = Competing at the same or higher level as when symptoms began   Points: ☐

8. Please complete **EITHER A, B or C** in this question.
 - *If you have no pain while undertaking Achilles tendon loading sports, please complete **Q8A only**.*
 - *If you have pain while undertaking Achilles tendon loading sports but it does not stop you from completing the activity, please complete **Q8B only**.*
 - *If you have pain which stops you from completing Achilles tendon loading sports, please complete **Q8C only**.*

A. If you have no pain while undertaking Achilles tendon loading sports, for how long can you train/practice?
  0 = Nil   1-10 mins = 7   11-20 mins = 14   21-30 mins = 21   >30 mins = 30   Points: ☐

OR

B. If you have some pain while undertaking Achilles tendon loading sports, but it does not stop you from completing your training/practice, for how long can you train/practice?
  0 = Nil   1-10 mins = 4   11-20 mins = 10   21-30 mins = 14   >30 mins = 20   Points: ☐

OR

C. If you have pain that stops you from completing your training/practice in Achilles tendon loading sports, for how long can you train/practice?
  0 = Nil   1-10 mins = 2   11-20 mins = 5   21-30 mins = 7   >30 mins = 10   Points: ☐

TOTAL SCORE (/100): ☐

Appendix 7

Studies Investigating HVUGI for the management of non-insertional achilles tendinopathy

Authors	Subjects	Intervention	Outcome measure	Outcome/ results
Chan et al., (2008)	30 (26 males, 4 females). Mean age 37.2 years. Failure to respond to 3 month eccentric loading programme. Athletically active No control group	Ultrasound guided injection (10ml 0.5% bupivacaine, 25mg hydrocortisone, 40ml injectable saline) +eccentric loading programme	Retrospective VISA-A / Study specific questionnaire using VAS. Subjects to complete 1st VISA-A questionnaire recalling symptoms immediately prior to ultrasound guided injection. 2nd VISA–A questionnaire on the day they returned questionnaire. Study specific questionnaire recall symptoms before and 2 weeks after injection	70% response rate VISA-A immediately prior to injection 44.8$\pm$ 17.7. Post injection 76.2$\pm$ 24.6. Mean follow up 30.3 weeks 2 weeks post injection VAS score mean change of 50mm from 76mm$\pm$ 18.2 to 25mm $\pm$ 23.3
Humphrey et (2009)	11 (7 males, 4 females). Mean age 43.5 years. Failure to respond to 3 month eccentric loading programme. Regular participation in sport No control group	Ultrasound guided injection (10ml 0.5% bupivacaine, 25mg hydrocortisone, 40ml injectable saline)	VISA-A questionnaire administered at baseline /3 weeks Neovascularity score baseline /3 weeks Tendon thickness baseline / 3 weeks	Baseline VISA-A 46.3$\pm$ 15.1 3 week VISA-A 84.1$\pm$ 10.6 Tendon thickness decreased from 8.7mm$\pm$ 2.0mm to 7.6mm$\pm$ 2.1mm Neovascularity score decreased from 3$\pm$ 1.1 at baseline to 1.1$\pm$ 1 at 3 weeks
Resteghini and Yeoh (2012)	32 (20 males, 12 females). Mean age 40.3 years No control group	Ultrasound guided injection (5ml 1% lignocaine, 25mg hydrocortisone , 40mg injectable saline	VISA-A questionnaire administered baseline/ 1 month/ 3 months VAS baseline / 1 month /3 month Tendon thickness baseline /1 month /3 months Neovascularity baseline /1 month / 3 months	VISA-A score Baseline mean 37.2 1 Month mean 63.7 3 Month mean 65.9 VAS Baseline 66 1Month 32 3Month 29 Tendon thickness Baseline 8.4mm 3Month 5.9mm Neovascularity Baseline 2.3 3Month 1.1
Maffulli et al (2013)	94 (69 men, 25 women). Mean age 37.5 years. Failure to respond to 3 month eccentric loading programme / other conservative measures. Participate in sport at least twice a week. No control group	Ultrasound guided injection (10ml 0.5% bupivacaine, 25mg Aprotinin, 40ml injectable saline 2nd injection if symptoms persist at two weeks. Aprotinin replaced with 25mg of hydrocortisone	VISA-A questionnaire administered at baseline / I year Tendon thickness baseline /1 year Neovascularity score baseline /1 year	Baseline VISA-A score 41.7$\pm$ 23.2 12 month VISA –A Score 74.6$\pm$ 21.4 Baseline tendon thickness 9.1mm $\pm$ 2.1mm 12 month tendon thickness 7.3mm $\pm$ 1.8mm Baseline neovascularity score 3$\pm$ 1.3
				12month neovascularity score 2.1$\pm$ 1.1

Wheeler (2014)	16 (7men and 9 women). Mean age 52.5 years Previous exercise therapy /orthoses	Ultrasound guided injection (10ml 1% lignocaine, 40ml injectable saline	VISA-A questionnaire administered at baseline and at review VAS- Baseline and follow up.	(14 with follow up data as review of two patients at only 3weeks) Average follow up of 347 days. Baseline VISA-A score 32 6-12 month VISA-A score 85 VAS Baseline 76.3mm VAS 6-12 months 23.3mm
Boesen etal., (2019)	28 men (18-59) 14 in each group. Of the 28 subjects 23 participated in sport. Only 3	Randomised Control trial – Double blinded –HVUGI group with steroid /group without steroid. Plus 40ml of injectable saline and 10ml of 0.5% bupivacaine and eccentric loading exercise plan post injection	VISA-A and VAS at baseline, 6 weeks, 12 weeks and 24 weeks. Tendon thickness and neovascularity measured.	HVUGI with steroid – VISA-A 6 weeks increase mean 30.6 ± 2.8 points from baseline VISA-A 12 weeks increase mean 31.9 ± 4.5 points from baseline VISA-A 24 weeks 26.4 ± 5.3 HVUGI without steroid VISA- A 6 weeks increase mean 13.8 ± 4.1 VISA-A 12 weeks increase mean 14.8 ± 3.1 VISA-A 24 weeks 23.7 ± 3.3 Tendon thickness and neovascularity reduced more in steroid group at 6 and 12 weeks
Gronbech-Nielson et al (2020)	28 (23 men,5 women) Failed 12 weeks of Eccentric Loading Exercise.	Ultrasound guided injection (10ml of 0.25% bupivacaine, 0.5ml Triamcinolonacetonide) plus 40ml of salline	VISA-A questionnaire administered at baseline and at 12 months	Retrospective study – Baseline VISA-A score 50 ± 15 12 month VISA A score 61 ± 21. 10 Patients no satisfied

Table illustrating Studies investigating high volume ultrasound guided injections for the management of non-insertional Achilles tendinopathy

Appendix 8

Studies Investigating eccentric loading exercise programmes for the management of noninsertional Achilles tendinopathy

Author	Subjects	Intervention	Outcome measures	Results / outcome
Curwin and Standish (1986)	200 patients with chronic achilles tendinitis. No other data provided	6 week exercise programme consisting of stretching followed eccentric loading followed by stretching. Eccentric exercises programme has increasing speed and resistance	Relief of pain –No PROM reported.	44% had complete relief of pain and functional impairment. 43% had marked decrease in symptoms.9% no change in their clinical state and 2% worse after exercise plan
Alfredson (1998)	15 Recreational athletes (12men 3 women) mean 44.3 years. 15 recreational athletes comparison group treated conventionally not randomised	12 week eccentric loading exercise plan versus comparison group which received – rest, NSAID, change of footwear, physical therapy.	Visual Analogue scale for pain at baseline and at 12 week. Calf strength at baseline and 12 weeks	Eccentric loading group- reduction in VAS from 81.2 $\pm$ 18 to 4.8 $\pm$ 6.5. Increase in calf strength from baseline to 12 weeks. All returned to pre injury levels of activity Comparison group – reduction in VAS from 71.8 $\pm$ 17.9 to 21.2 $\pm$ 11.4. No increase in strength from baseline to 12 weeks. All required surgery
Silbernagel et al., (2001)	40 Patients (57 tendons) mean age 45 years (31 men and 9 women)	Group 1 12 weeks of eccentric loading group 2 concentric exercise plan	Visual Analogue Scale for pain at baseline, 6 weeks, 3 months and 6 months	Decrease in VAS score in both groups (28 points in eccentric group and 18 points in concentric group). 60% of eccentric group full recovery. 25% in concentric group
Mafi et al., (2001)	44 patients referred with severe Achilles tendinopathy. Randomly assigned to two groups consisting of 22 patients each. Group one carried out eccentric exercises (12 men 10 women with a mean age of 48 $\pm$ 9.5 years). Group 2 carried out concentric exercises (12 men 10 women with a mean age of 48 $\pm$ 8.3 years)	Group 1 eccentric loading exercise programme as described by Alfredson for 12 weeks. Group 2 series of concentric exercises (dynamic exercise included)	Visual Analogue Scale for pain at baseline and at 12 weeks. Satisfaction / return to activity	Eccentric loading group 82% of patients 18/22 were satisfied and returned to activity. In those patients who were satisfied the VAS score reduced from 69 at baseline to 12 post treatment. In the 4 who were not satisfied psot intervention VAS score was 44. In the In the concentric exercise group 36% were satisfied and returned to activity 8/22. Their VAS score reduced from 63 at baseline to 9 post intervention. The 14 who were not satisfied their post intervention VAS score was 60.

Fahlstrom et al., (2003)	78 (101 tendons) consecutive recreational athletes with mid portion Achilles tendinopathy (55 men and 23 women) mean age 46.1± 9.5 (101 tendons) and 30 consecutive patients with insertional Achilles tendinopathy (24 men and 6 women) mean age 37.9 ± 11.6 years.(31 tendons)	12 eccentric loading exercise plan with progressive loading Light physical activity allowed during 12 weeks but at a level which produced only mild pain and discomfort	Visual Analogue Scale at baseline and at 12 weeks	In the group with mid portion Achilles tendinopathy those who returned to preinjury activity (68 patients / 90 tendons) VAS score reduced from 66.8 ± 19.4 to 10.2 ± 13.7. in the 10 patients where there was poor result VAS score reduced from 74 ± 18.9 to 64.9 ± 26.4.
Sayana and Maffulli (2006)	34 sedentary patients (18 men and 16 women) Mean age of the men 44 years (23-67) and the mean age of the women 51 (20-76)	Patient presenting with unilateral Achilles tendinopathy – mean duration of symptoms was 13.9 ± 8.2 months (6-31 months). Carried out graded eccentric exercise programme for 12 weeks	VISA-A score was recorded at the pre-management stage and at mean follow up which was 15 ± 7.3 months	The mean VISA – A score pre management was 39 ± 22.8 and was a mean of 50 ± 26.5 at a latest follow up. 19 of the 34 patients responded to the eccentric loading exercise plan and were discharged. 15 did not improve with eccentric loading with 7 going on to have surgery
Maffulli et al., (2008)	45 athletic patients (29 men and 16 women). Mean age of the men was 26 ± 12.8 years and the mean age of the women 28 ± 13.1 years	Patients presenting with unilateral Achilles tendinopathy – mean duration of symptoms 16.4 ± 9.2 months (7-31 months). Carried out graded eccentric exercise programme for 12 weeks. Reviewed every 2 weeks in outpatients and contacted every week by the research nurse to encourage completion of the exercises	VISA – A score was recorded, at the pre-management stage and at week 12.	The mean VISA-A score pre management was 36 ± 23.8 and improved to 52 ± 27.5. 27 of the 45 responded to the exercise programme. 18 who did not improve were given aprotinin injections. Five improved with injection, 10 proceeded to surgery and 3 declined surgery.
Stasinopoulos and Manias (2012)	41 patients with midportion Achilles tendinopathy for at least 3 months. Allocated to two groups. Stanish group mean age 48.44 ± 5.12, Alfredson group mean age 48.24 ± 5.09 years	Sequentially allocated into two groups one following the Stanish exercise programme (n=21) and the other the Alfredson exercise programme (n=20) Both include eccentric loading for 12 weeks	VISA- A score of both groups at baseline, week 12 and week 36.	Baseline VISA score for Stanish group was reported as a mean of 38 (28-48). At week 12 a mean score of 63 (5773) and at week 36 a mean score of 64 (5879) Baseline VISA score for the Alfredson group was a mean 36 (27-47). At week 12 a mean score of 76 (77-90) and at week 36 a mean score of 78 (75-94)

Table illustrating studies investigating the effect of eccentric loading exercises for the management of non-insertional Achilles tendinopathy Appendix 9
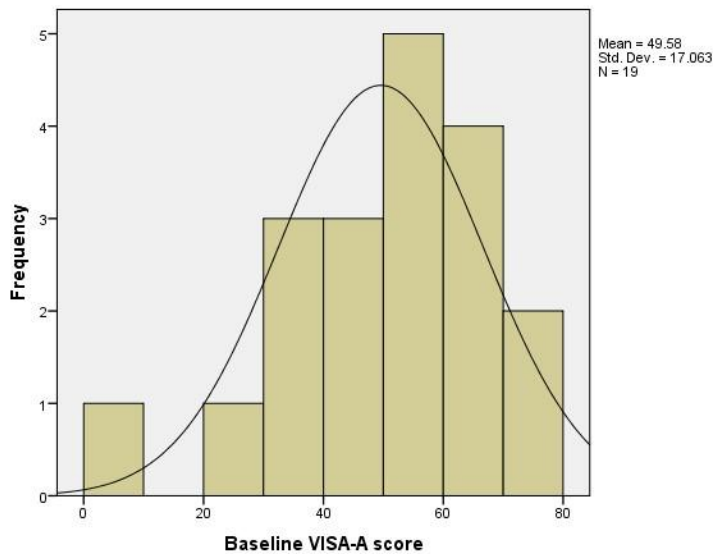
Baseline VISA- A score test for normality

Figure 1 a histogram illustrating the distribution of the baseline scores for the VISA-A questionnaire with superimposed distribution curve for the control group (ELE group)

The histogram in figure 1illustrates the superimposed distribution curve which is a typical bell curve shape suggestive of normally distributed scores.
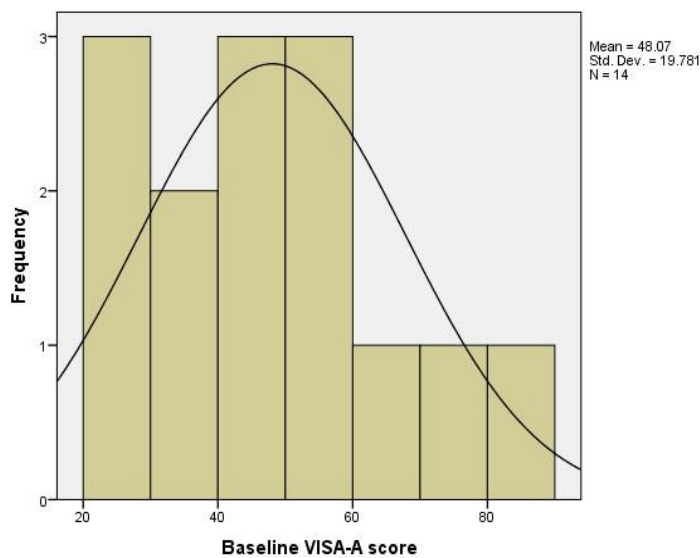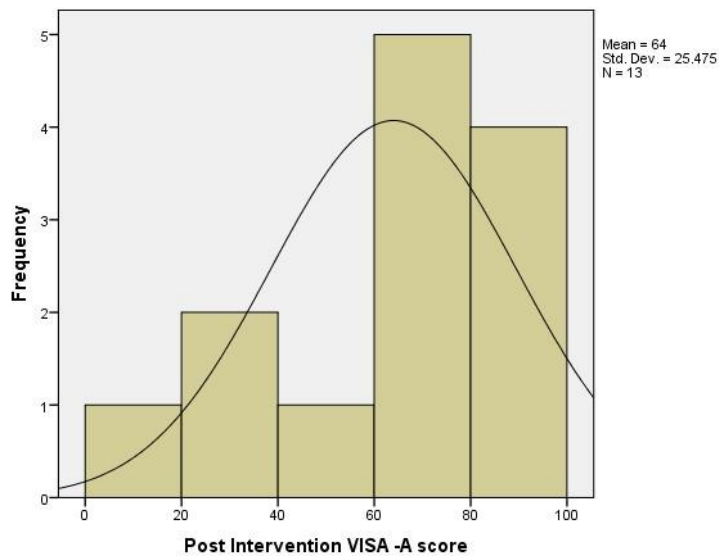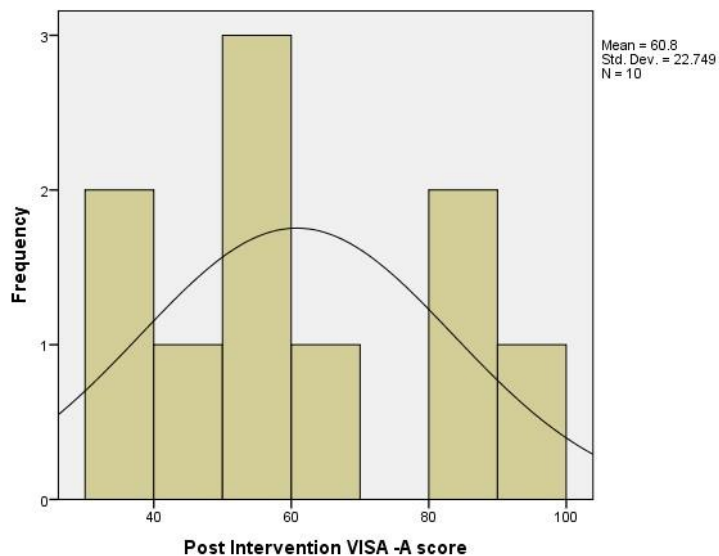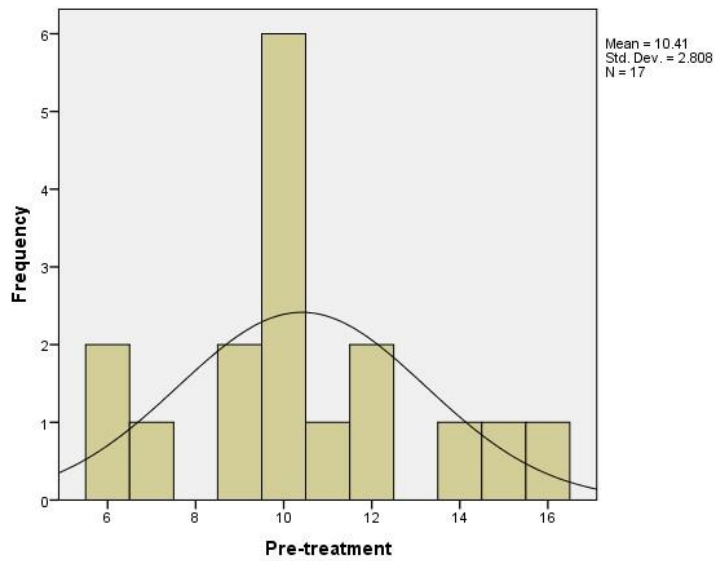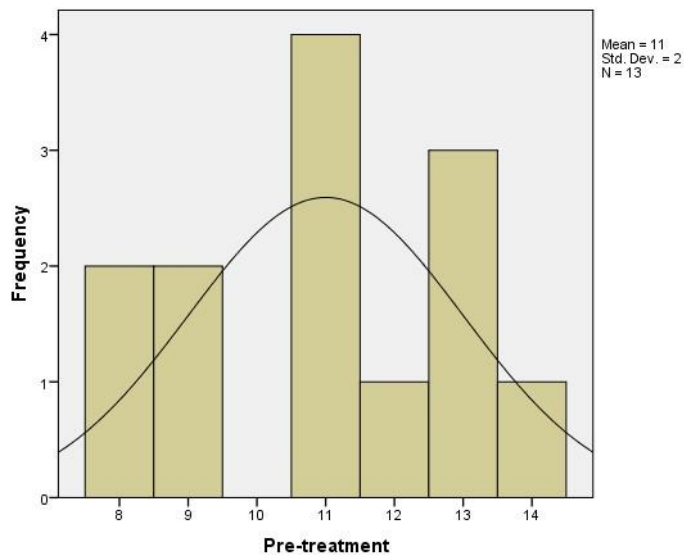

Figure 2 a histogram illustrates the distribution of the baseline scores for the VISA – A questionnaire with superimposed distribution curve for the treatment group (HVUGI group)

The histogram in figure 2 illustrates the superimposed distribution curve which is a typical bell curve suggestive of normally distributed data. **Post Intervention VISA- A score test for normality**

Figure 3 a histogram which illustrates the distribution of the post intervention scores for the VISA – A questionnaire with superimposed distribution curve for the control group (ELE group)

The histogram in figure 3 illustrates the superimposed distribution curve which is a typical bell curve shape suggestive of normally distributed scores.
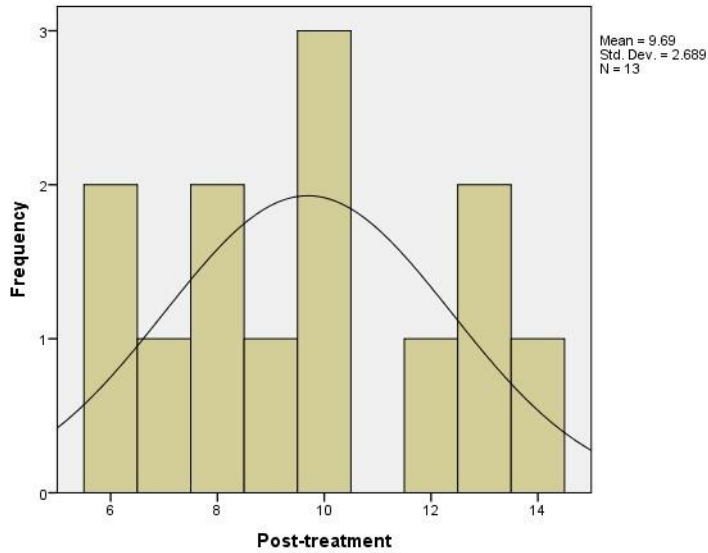

Figure 4 - a histogram which illustrates the distribution of the post intervention scores for the VISA - A questionnaire with superimposed distribution curve for the treatment group (HVUGI group)

The histogram in figure 5 illustrates the distribution of the post intervention the superimposed distribution curve which is typical bell curve shape suggestive of normally distributed scores.

Tendon Thickness

Figure 5 illustrates the distribution of the measurement of Achilles tendon thickness measured in mm at baseline in the control (ELE Programme)

The histogram in figure 5 illustrates the distribution the superimposed distribution curve which is a typical bell curve shape suggestive of normally distributed scores.

Figure 6 illustrates the distribution of the measurement of Achilles tendon thickness in mm at baseline in the treatment group who received a High-Volume Ultrasound Guided Injection

The histogram in figure 6 illustrates the superimposed distribution curve which is a typical bell curve shape suggestive of normally distributed scores.
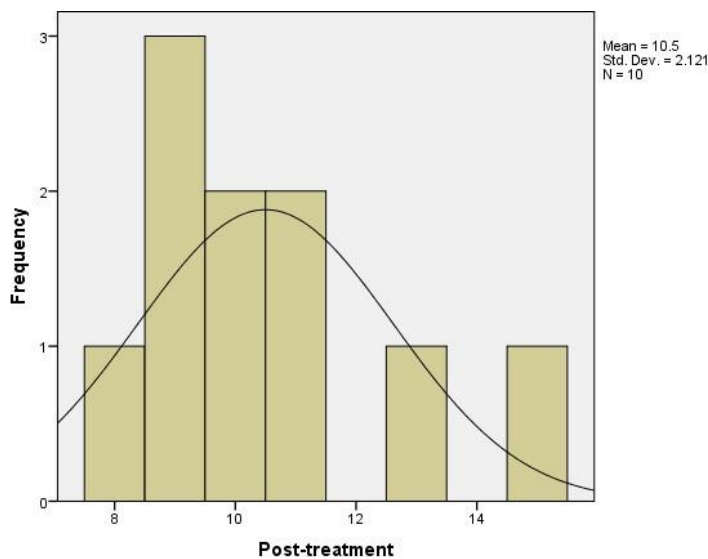
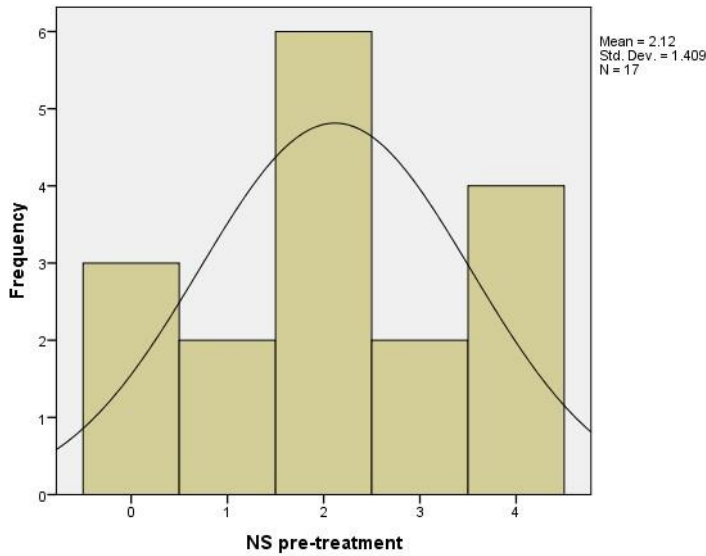**Figure 7 illustrates the distribution of the measurement of Achilles tendon thickness in mm post intervention in the control group who carried out an eccentric loading exercise plan.**

The histogram in figure 7 illustrates the superimposed distribution curve which is a typical bell curve shape suggestive of normally distributed scores.

Figure 8 illustrates the distribution of the measurement of Achilles tendon thickness in mm post intervention in the treatment group who received a High-Volume Ultrasound Guided Injection.

The histogram in figure 8 illustrates the superimposed distribution curve which is a typical bell curve shape suggestive of normally distributed scores.
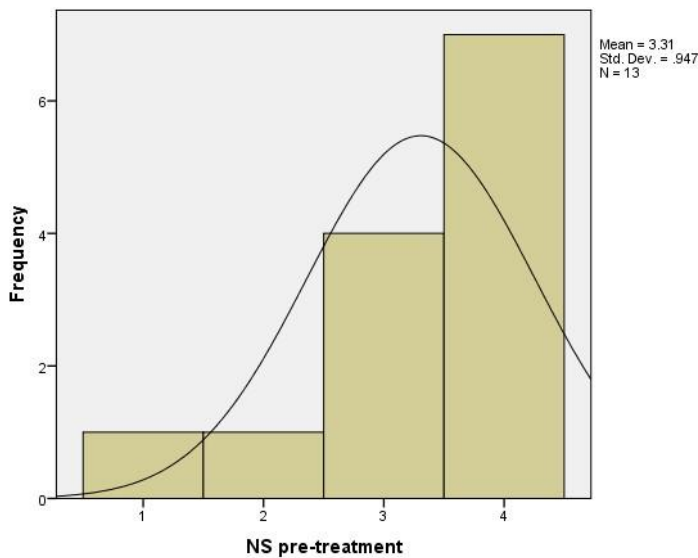
Neovascularity scores

Mean = 2.12
Std. Dev. = 1.409
N = 17

Figure 9 illustrates the distribution of scores for neovascularity (0-4) in the control group who carried out an Eccentric Loading Exercise Programme pre-intervention.

The histogram in figure 9 illustrates the superimposed distribution curve which is a typical bell curve shape suggestive of normally distributed scores.

Mean = 3.31
Std. Dev. = .947
N = 13

Figure 10 illustrates the distribution of scores for neovascularity (0-4) in the treatment group who received a High-Volume Ultrasound Guided Inject pre-intervention.

The histogram in figure 10 illustrates the superimposed distribution curve which shows a positively skewed bell curve suggestive of scores which are not normally distributed
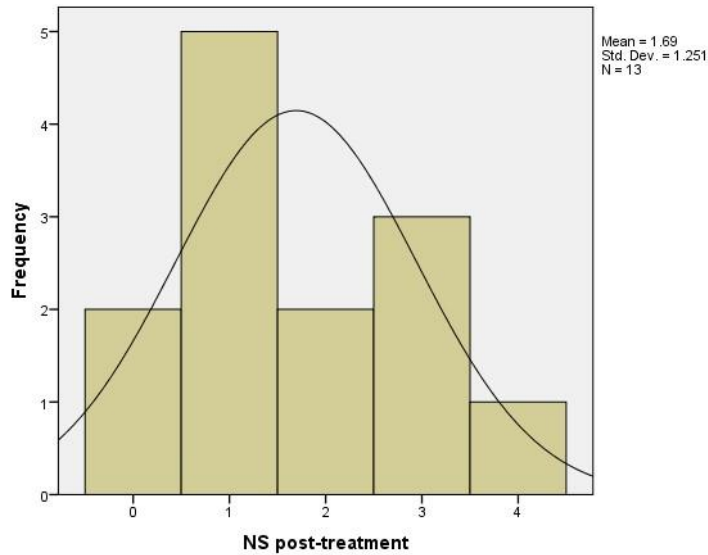
Figure 11 illustrates the distribution of scores for neovascularity (0-4) in the control group post intervention.

The histogram in figure 11 illustrates the superimposed distribution curve which shows a typical bell curve suggestive of normally distributed scores.
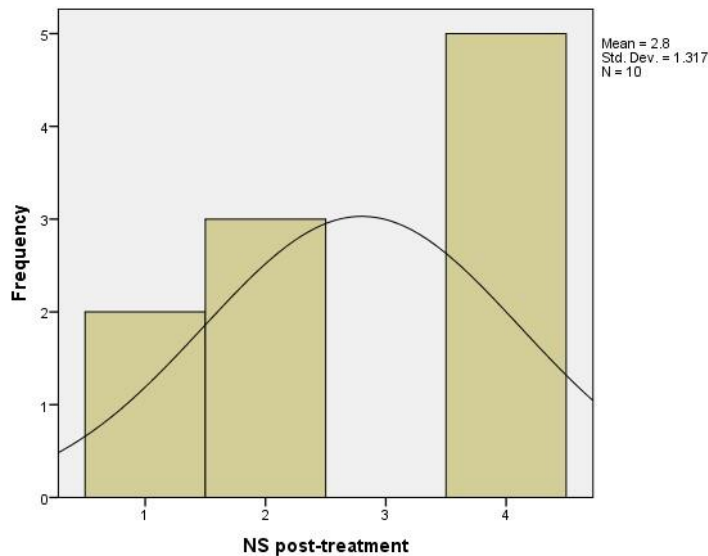

Figure 12 illustrates the distribution of scores for neovascularity (0-4) in the treatment group post intervention.

The histogram in figure 12 illustrates the superimposed distribution curve which shows a positively skewed bell curve suggestive of scores which are not normally distributed.

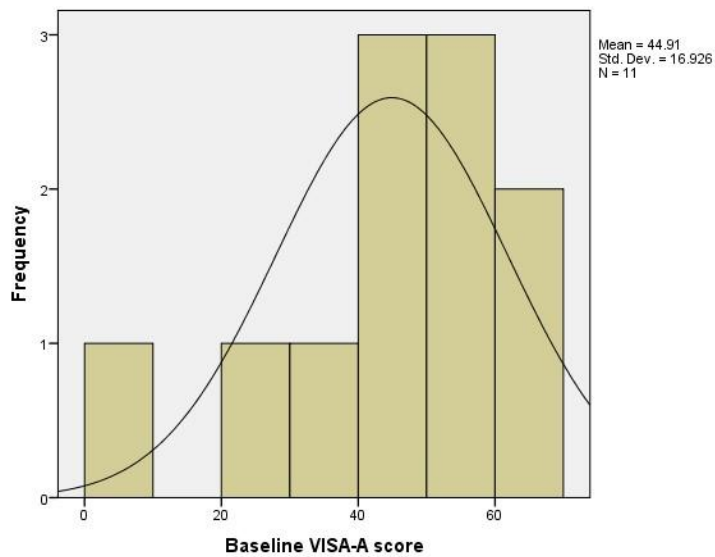**Baseline VISA-A score –test for normality (Complete data set)**

Figure 13 a histogram illustrating the distribution of the baseline scores for the VISA-A questionnaire with superimposed distribution curve for the control group (ELE group) for the complete data set.

The histogram in figure 14 shows the distribution of scores for the baseline VISA-A scores for the control group. The superimposed distribution curve shows normally distributed data.
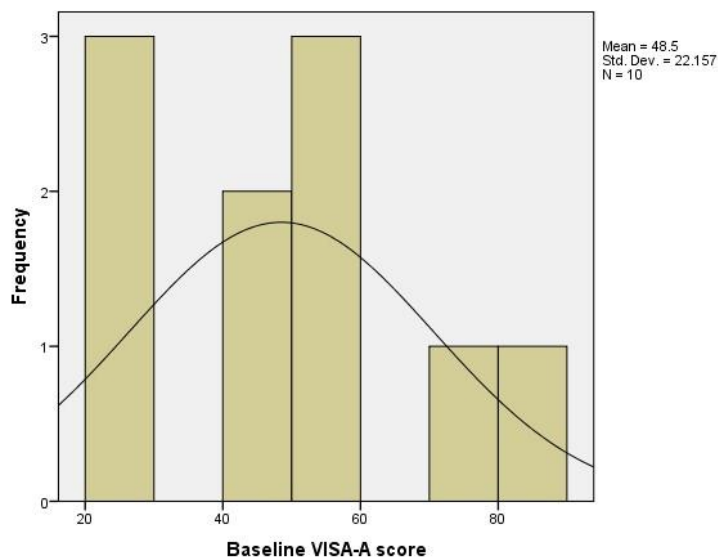

Figure 14 a histogram illustrating the distribution of the baseline scores for the VISA-A questionnaire with superimposed distribution curve for the treatment group (HVUGI group) for the complete data set.

The histogram in figure 14 shows the distribution of scores for the baseline VISA- A scores for the treatment group for which we had complete data. The superimposed distribution curve shows the typical bell curve suggestive of normally distributed data.

Post Intervention VISA-A score test for normality
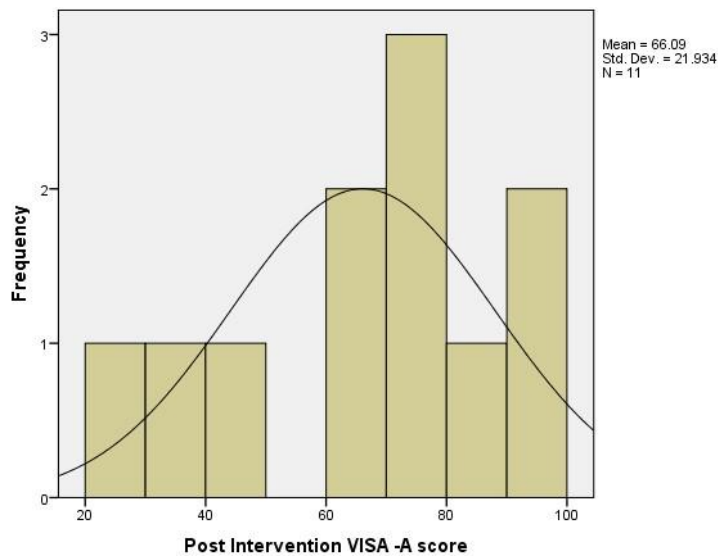

Mean = 66.09
Std. Dev. = 21.934
N = 11

Figure 15 a histogram illustrating the distribution of the post intervention scores for the VISA-A questionnaire with superimposed distribution curve for the control group (ELE group) for the complete data set.

The histogram in figure 15 illustrates the post intervention VISA-A scores for the participants in the control group for which there was complete data. The superimposed distribution curve shows the typical bell curve shape suggestive of normally distributed data
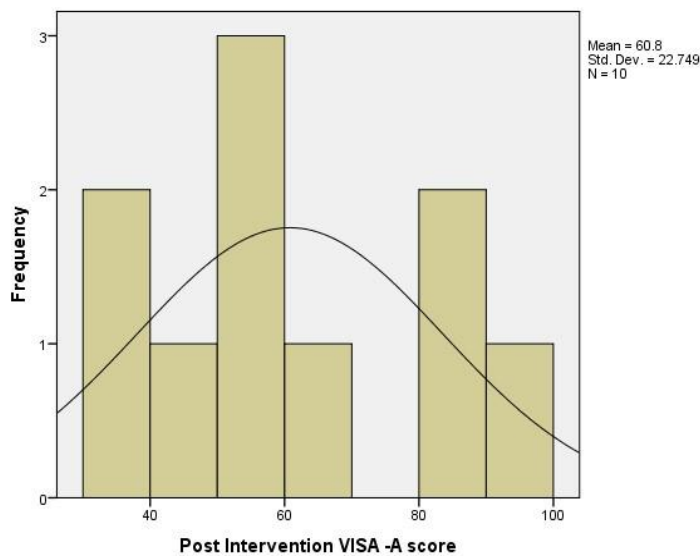

Mean = 60.8
Std. Dev. = 22.749
N = 10

Figure 16 a histogram illustrating the distribution of the post intervention scores for the VISA-A questionnaire with superimposed distribution curve for the trial group (HVUGI group) for the complete data set.

Figure 16 illustrates the post intervention VISA-A scores for those participants in the trial group for which there is complete data. The superimposed distribution curve shows the typical bell curve suggestive of normally distributed scores.

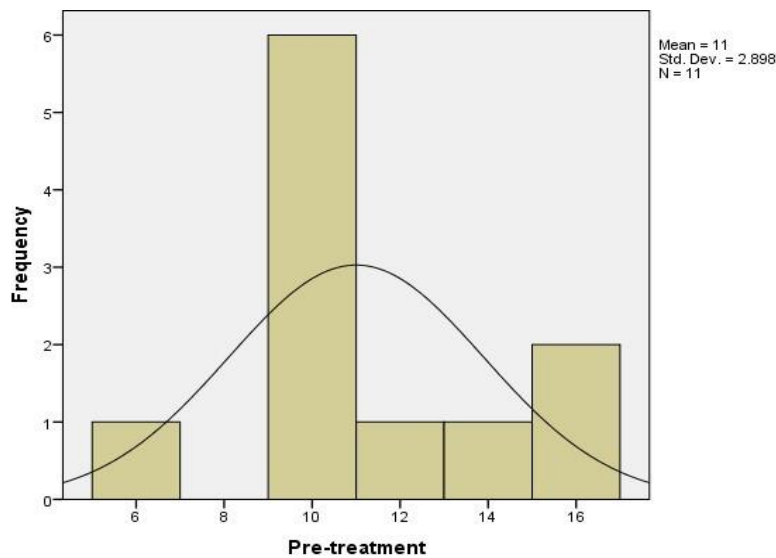**Pre intervention Tendon thickness- test for normality**

Figure 17 illustrates the distribution of the measurements of Achilles tendon thickness (mm) pre-treatment in the control group (ELE) for the complete data set

Figure 17 illustrates the distribution of the pre-treatment measurements of tendon thickness for the control group where there was complete data available. The superimposed distribution curve shows the typical bell curve suggestive of normally distributed scores.
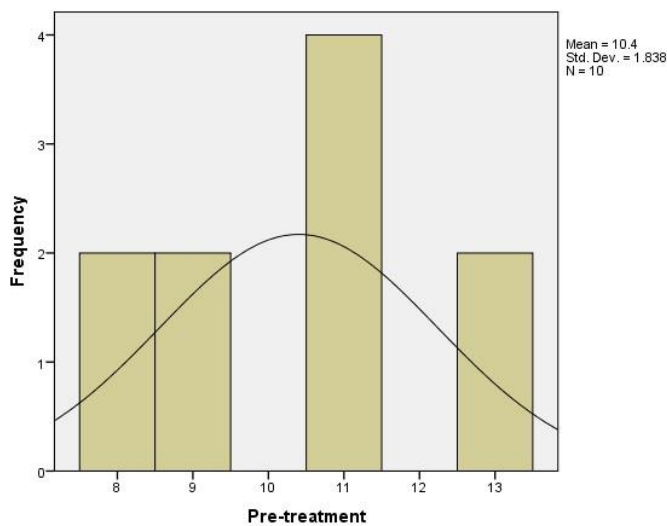

Figure 18 illustrates the distribution of the measurements of Achilles tendon thickness (mm) pre-treatment in the trial group (HVUGI group) for the complete data set

Figure 18 illustrates the distribution of the pre-treatment measurements of tendon thickness for the trial group where there was complete data available. The superimposed distribution curve shows the typical bell curve suggestive of normally distributed scores.

Post Intervention tendon thickness measurements –test of normality

Mean = 10.27
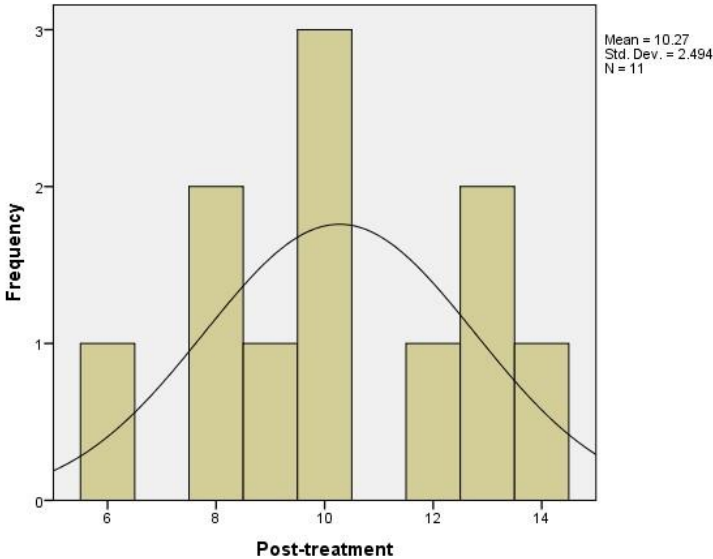Std. Dev. = 2.494
N = 11

Figure 19 illustrates the distribution of the measurements of Achilles tendon thickness (mm) post treatment in the control group (ELE) for the complete data set

Figure 19 illustrates the distribution of the post-treatment measurements of tendon thickness for the control group where there was complete data available. The superimposed distribution curve shows the typical bell curve suggestive of normally distributed scores.

Mean = 10.5
Std. Dev. = 2.121
N = 10

Figure 20 illustrates the distribution of the measurements of Achilles tendon thickness (mm) post treatment in the treatment group (HVUGI) for the complete data set.

Figure 20 illustrates the distribution of the post-treatment measurements of tendon thickness for the treatment group where there was complete data available. The superimposed distribution curve shows the typical bell curve suggestive of normally distributed scores.
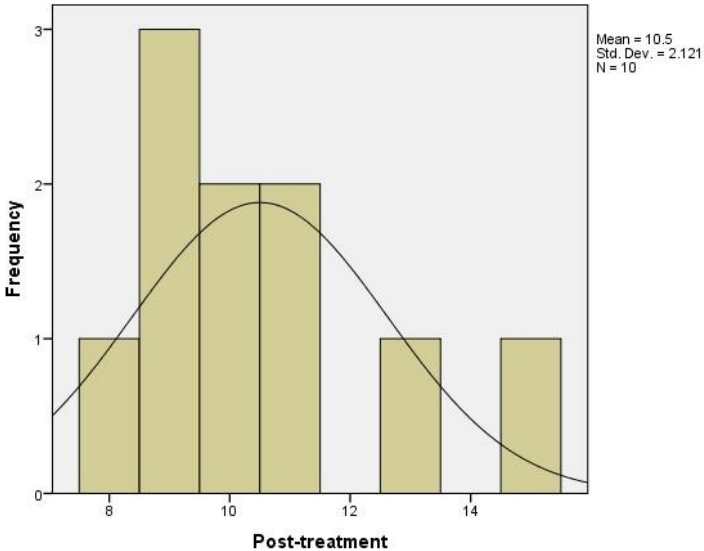
Pre-Intervention neovascularity score – test for normality

Figure 21 Illustrates the distribution of scores for neovascularity (0-4) in the control group who carried out an Eccentric Loading Exercise Programme pre-intervention for the complete data set.

Figure 21 illustrates the distribution of the pre-intervention neovascularity scores for the control group. The superimposed distribution curve shows the typical bell curve suggestive of normally distributed scores.

Figure 22 illustrates the distribution of scores for neovascularity (0-4) in the treatment group (HVUGI group) pre-treatment for the complete data set.

Figure 22 illustrates the distribution of the pre-intervention neovascularity scores for the trial group. The superimposed distribution curve shows a positively skewed bell curve suggestive of scores which are not normally distributed.
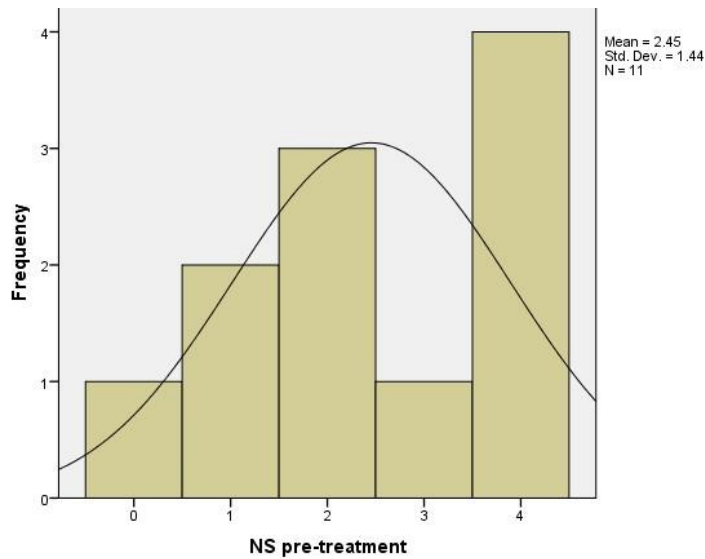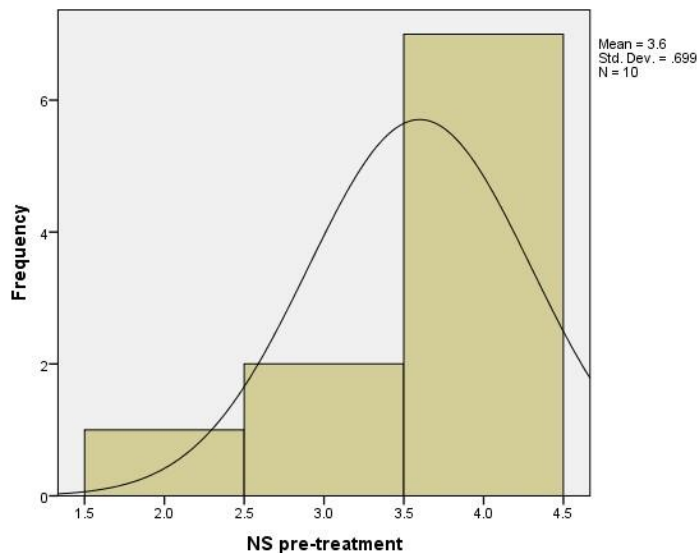

Figure 23 Illustrates the distribution of scores for neovascularity (0-4) in the control group who carried out an Eccentric Loading Exercise Programme post-treatment for the complete data set.

Figure 23 illustrates the distribution of the post-intervention neovascularity scores for the control group. The superimposed distribution curve shows a negatively skewed bell curve suggestive of scores which are not normally distributed.

Figure 24 illustrates the distribution of scores for neovascularity (0-4) in the trial group who received a high-volume ultrasound guided injection (HVUGI) post-treatment for the complete data set.

Figure 24 illustrates the distribution of the post-intervention neovascularity scores for the trial group. The superimposed distribution curve shows a positively skewed bell curve suggestive of scores which are not normally distributed.
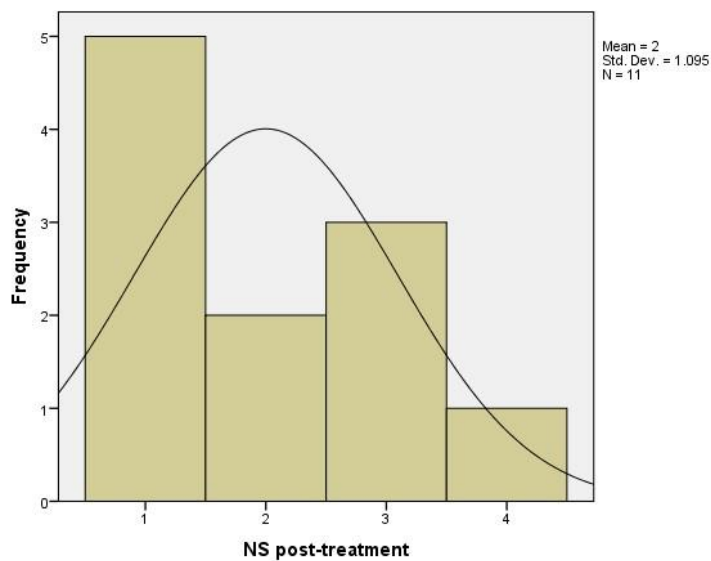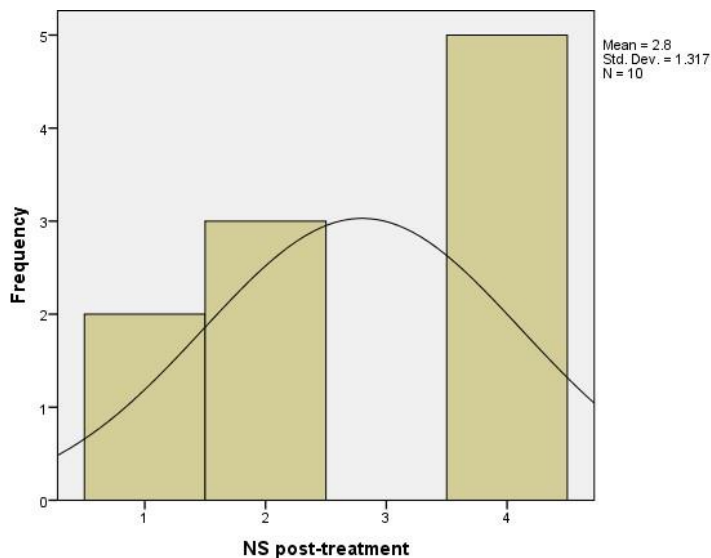

Appendix 10 Draft manuscript

Treating Achilles tendon pain – A feasibility study of High-Volume Ultrasound Guided Injections Verses Eccentric Loading Exercises

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Abstract Background

Non-insertional Achilles tendinopathy is a common overuse injury which affects the midportion of the Achilles tendon. It is often seen in patients between the age of 30-50 years who take part in sport or other physically demanding leisure or work activity. It is characterised by pain, impaired function and swelling around the affected tendon. The most common nonoperative treatment is an eccentric loading exercise programme which has been shown to give variable short and long-term results. However, the eccentric exercise programme is long (12 weeks), laborious (twice a day 7 days per week) and painful to perform. As an alternative some authors have shown a reduction in pain and improved function by injecting a high volume of saline around the effected tendon under ultrasound guidance. Unfortunately, the quality of these studies was poor, with no Randomised Control Trials to date. Therefore, the aim of this study was to examine the feasibility of conducting a future RCT (Randomized Controlled Trial), comparing high volume ultrasound guided injections (HVUGI) of saline solution with eccentric loading exercises for the treatment of non-insertional Achilles tendinopathy.

Method

Thirty-three patients took part in a two-arm randomised feasibility study. They were individually randomised via an online computer-generated programme to either a treatment group who received a HVUGI or a control group who carried out a 12-week eccentric loading exercise programme. Primary outcomes included eligibility rate, recruitment rate, retention rate and adverse events. Secondary outcomes included measuring the effect on pain and function of HVUGI compared with eccentric loading exercises using the VISA-A (Victoria Institute of Sport Assessment Achilles) patient reported outcome measure. In addition, the effect of the treatment and control interventions on tendon thickness and neovascularity were measured. In the control group, adherence to the exercise regime was measured through a self-reported diary.

Results

During a six-month period 63 patients were referred to the department of orthopaedics in a large Scottish Teaching Hospital with Achilles tendon pain. Of those 43 (68%) were considered eligible and 33 (77%) agreed to take part in the study. Of the 33 randomised (treatment group

=14, control group 19) two were excluded because of abnormal ultrasound scans. Eight subjects were lost to follow-up at 12 weeks resulting in a retention rate of 74% (n=23). Adherence to the eccentric loading programme was 74% when recording the number of exercise sessions completed as a percentage of the total suggested. Although improved function and reduced pain were seen in both groups, reflected by an increase in the mean VISA-A score, no significant difference was noted between the groups. No differences were seen in the secondary physiological measurements of tendon thickness and neovascularity either. However, caution regarding the outcome measures should be exercised due to the small sample size.

Conclusion

This study identified some key issues which could challenge the feasibility of carrying out a future RCT. This included issues around recruitment, retention, and adherence to the eccentric loading exercise programme. It was also observed that this study failed to assess any early improvements in function and reduction in pain when comparing the control and treatment group which should be addressed in any future study. Therefore, it is suggested that a pilot study is carried out with modifications made to improve areas of deficit and implement changes which include earlier evaluation of pain and function. Only if these areas show improvement to an agreed threshold should a future RCT be considered.

Trial registration ISRCTN11851359 Keywords

VISA-A, HVUGI (High Volume Ultrasound Guided Injection), ELE (eccentric loading exercises)

Background

Non- insertional Achilles tendinopathy is a common overuse injury most frequently seen in patients between the ages of 30-50 years who actively take part in sport or other physically demanding leisure or work activities (1). Although most seen in the physically active it is also reported in the more sedentary, with reported estimates of around 33% of all cases occurring in those who participate in little or no regular exercise (2). The incidence of non-insertional Achilles tendinopathy in the athletic and general population has tended to be reported separately with the incidence reported in athletes ranging from 7.4% to 9% (3, 4), whilst general population studies report an incidence of around 2.35 per 1000

Non-insertional Achilles tendinopathy has been described as a clinical triad of pain, impaired function and swelling (thickening of the tendon) in and around the Achilles tendon (Longo et al.,2009). This clinical triad is often accompanied with loss of normal collagenous architecture and neural and vascular ingrowths (neovascularity). Pain is the cardinal symptom which is principally associated with loading of the tendon during activity. Although, the primary focus of any treatment intervention should be a reduction in pain to help improve function and facilitate early mobilisation, changes in tendon thickness and neovascularity are often evaluated. Several studies have showed an association between a reduction in pain and improved function with a reduction in neovascularity and swelling (5,6,7). However, this is contrary to a more recent systematic review which failed to find a similar correlation (8).

A wide variety of treatment approaches, both non-surgical and surgical, have been described in the literature. Currently the mainstay of non-surgical management is eccentric loading exercises which have been shown to provide variable short and long-term results. The effectiveness of these exercises appears to vary between athletic and non-athletic populations, with results ranging from 82% in athletic patients (9) compared to 54% in non-athletic patients

(10). Irrespective of these variations in effectiveness eccentric loading exercises continue to provide an option requiring minimal clinical intervention. However, the eccentric loading programme developed by Alfredson and his colleagues in 1998 (11) and the one currently preferred in practice is long (12 weeks), laborious (twice a day 7 days per week) and painful to perform, characteristics which raise issues of adherence and the ability of some individuals to perform the exercises. Therefore, an alternative non-surgical treatment could be a valuable adjunct to the management of non-insertional Achilles tendinopathy. The use of high-volume ultrasound guided injections (HVUGI) has gained some popularity as an alternative treatment choice. This intervention involves injecting a large volume (40ml) of injectable saline around the Achilles tendon under ultrasound guidance. The injection is thought to produce mechanical disruption that stretch, break, or occlude the neovessels associated with pain (12). As injectable saline is an inert isotonic substance (similar concentration to body fluid) the risk of adverse reactions should be less than other pharmaceutical agents which have been injected around a painful Achilles tendon.

Several studies have reported on the use of HVUGI and have all showed positive results with regards to reduced pain and improved function. However, the case series approach adopted by all but one study, the use of different injection regimes and different measurement points make direct comparison between studies difficult. The lack of a control group is considered a weakness in this type of study design as it does not eliminate the effect of any extraneous variables which could have a confounding effect on the results.

Therefore, considering the need to address the weaknesses highlighted an RCT would seem to address many of these issues and increase the internal validity. However, RCT'S can be costly and time consuming to carry out with many not recruiting enough subjects or able to retain subjects throughout the duration of the study. Consequently, the Medical Research Council guidelines for complex interventions recommends that as part of the planning and development process for an RCT some feasibility work is conducted to show if the study can be carried out and if so how. Therefore, as recommended this study aimed to assess the feasibility of carrying out a future RCT.

The introduction of a control group treated with the standard treatment (eccentric loading exercise programme) currently used in practice, and random allocation of subjects to either the control or treatment group, aimed to help eliminate any cofounding effects and reduce selection bias which was identified as a methodological weakness and threat to the internal validity of the earlier studies on the use of HVUGI. Recruitment was based on a set of clearly defined inclusion and exclusion criteria. The inclusion criteria were key features of the target population whilst exclusion criteria helped minimise random error, selection bias and confounding.

Aims and Objectives

Aims

The aim of this study was to assess the feasibility of a future definitive randomised trial to compare HVUGI with eccentric loading exercises in reducing pain and improving function in subjects with non-insertional Achilles tendinopathy

Primary objectives

The primary objectives detailed below were developed to assess the feasibility of study processes including rates of participant recruitment, retention, and safety.

- To calculate the eligibility rate- the number of eligible subjects as a proportion of the total screened patients in a three-month period.
- To calculate the recruitment rate- the number of recruited patients as a proportion of the number of eligible patients within the three-month period.
- The test the proposed method of randomisation to achieve an even balance of subject numbers in each arm of the study.
- To evaluate adherence with the intervention- the eccentric loading group are required to carry our painful exercises for 12 weeks- adherence was evaluated with the use of an adherence diary which was completed by the subject and recorded frequency (number of sessions per week) and intensity (number of repetitions per session).
- To evaluate follow up rates- the total number of recruited subjects who are followed to the end of the study period.
- Evaluate the outcome measures utilised in the study- VISA-A questionnaire / Ohbergs modified neovascularity score.
- Record any adverse reactions to the HVUGI or the eccentric loading programme.

Secondary objectives

The secondary objectives were developed to explore trends in treatment effect

- Describe the effect of high-volume ultrasound guided injections compared with eccentric loading on pain and function in subjects with non-insertional Achilles tendinopathy.
- Describe the effect of high-volume ultrasound guided injection compared with eccentric loading on tendon thickness in subjects with non-insertional Achilles tendinopathy.
- Describe the effect of high-volume ultrasound guided injections compared with eccentric loading on neovascularity in subjects with non-insertional Achilles tendinopathy.

No hypothesis testing was carried out as part of this feasibility study as recruitment rates were part of the primary outcomes measures and will determine the necessary sample size needed to carry out a larger scale study suitable powered to 0.8 with a level of significance of ≤ 0.05.

Materials and methods

This two-arm randomised feasibility study was conducted at Edinburgh Royal Infirmary Department of Orthopaedics and Trauma. The study protocol was prospectively registered with ISRCTN (ISRCTN11851359) whilst ethical approval was granted by Southeast Scotland REC (REC no 17/55/0107). The report conforms to the Consolidated Standards of Reporting Trials (CONSORT) extension to randomised pilot and feasibility trial guidelines.

Eligibility Criteria

- Ages 18 years or older
- Capacity to give informed consent

- Clinical diagnosis of non-insertional Achilles tendinopathy* / plus diagnostic ultrasound confirmation
- English language as a first language

Clinical diagnosis would include the following:

- *Pain and tenderness on palpation of the Achilles tendon 2-6cm from the insertion into the calcaneus.*
- *Evidence of tendon thickening on palpation of the Achilles tendon.*
- *Negative Simmonds-Thompson test (Test to exclude tendon rupture)*

Exclusion Criteria

Concurrent musculoskeletal problem- such as ankle sprains or osteoarthritic changes in the ankle

- Has a diagnosed rheumatological disorder such as Rheumatoid disease
- Suffered total or partial tear of the Achilles tendon
- Previous injection for non-insertional Achilles tendon
- Previous surgery to the Achilles tendon
- Patients with bilateral non insertional Achilles tendinopathy.
- Currently taking quinolone antibiotics (or in the prior 3 months)

Thirty-three patients took part in a two-arm randomised feasibility study. They were individually randomised via an online computer-generated programme to either a treatment group who received a HVUGI or a control group who carried out a 12-week eccentric loading exercise programme. Primary outcomes focused on eligibility, recruitment, retention, and adverse events. Secondary outcomes included measuring the effect on pain and function of HVUGI compared with eccentric loading exercises using the VISA-A (Victoria Institute of Sport Assessment Achilles) questionnaire as the patient reported outcome measure (PROM). In addition, the effect of the treatment and control interventions on tendon thickness and neovascularity were measured. In the control group, adherence to the exercise regime was measured through a self-reported diary. **Recruitment of participants**

Participants (n=33) were recruited from patients referred to the foot and ankle service at a large teaching hospital in Scotland, United Kingdom. Referrals were from General Practitioners (n=25) and other health care professionals including podiatrists (n=5) and physiotherapists (n=3).

All referrals to this service were triaged by a Consultant Podiatrist, who decided whether the patient was seen by a specialist podiatrist or consultant orthopaedic surgeon. The decision on the appropriate referral pathway was decided by the information provided by the referrer. Those patients suspected of having non-insertional Achilles tendinopathy were triaged to a specialist podiatrist in the direct care team. All patients referred in a six-month period with the clinical signs and symptoms of non-insertional Achilles tendinopathy (pain, impaired function and swelling in and around the Achilles tendon) were advised of the study (n=63). Of the 63 patients screened, 20 were excluded because of having pain and symptoms in both Achilles tendons, had undergone earlier treatment or their symptoms were suggestive of insertional Achilles tendinopathy. The remaining 43 eligible to enrol in the study were provided with written information about the study. In addition they were given the opportunity to discuss the study

with the Principal Investigator (PI), Of the 43 eligible to enrol 10 declined to take part. The 10 patients not interested in participating were treated following the local care pathway. The recruitment of participants is summarised in figure 1. Baseline measures on figure 1 refer to the administration of the VISA-A questionnaire and the measurement of neovascularity and tendon thickness.

Randomisation

The study randomly assigned participants into two groups. One group received the HVUGI (treatment group) whilst the other received the current standard intervention of an eccentric loading programme (control group). Randomisation was performed using the Sealed Envelope online randomisation programme (Sealed Envelope, London, UK). All eligible participants were given a unique 9-digit code which consisted of their date of birth plus a further three digits. The participant's unique identification code and names were stored separately on a password protected server which only the PI had access. The aim of storing them separately was to ensure anonymity of data collected. The participants were randomly distributed into the two groups using simple block randomisation block design (C). The block sizes were four, six, and eight. The use of different block sizes removed the ability of the researchers to be able to work out sequencing whilst trying to ensure equivalent group size (17). The randomisation system was accessed via a secure connection over the internet. This connection encrypted data between the PI's internet browser and the server. To achieve online randomisation the PI had to provide the participant's unique identification code, the PI's email address and the randomisation system password set when registering the study with Sealed Envelope. On receipt of this information, the system randomised the participant to treatment or control and notified the PI by email. For transparency participants were able to observe the process and see a copy of the returned email.
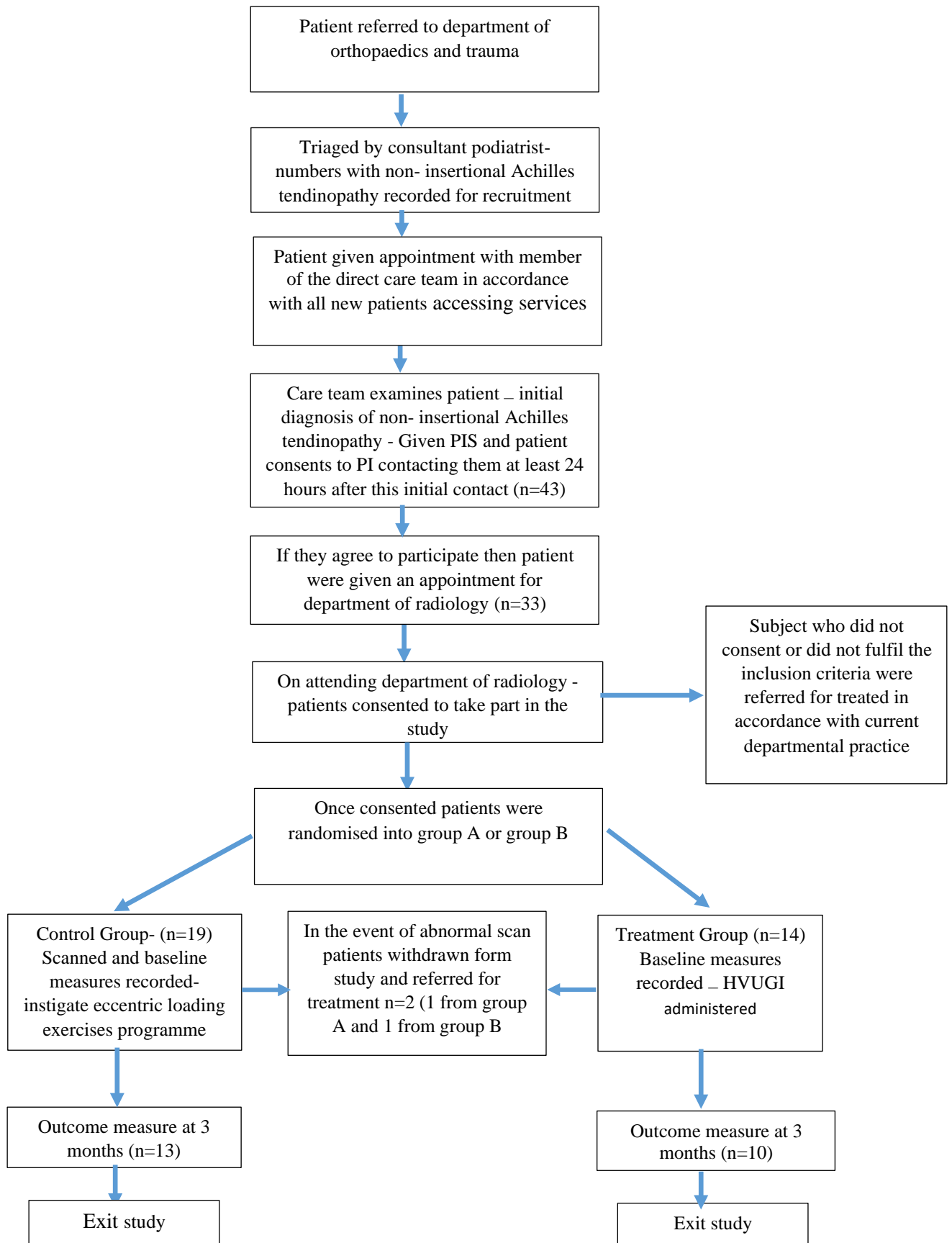
Figure 1 Participant study pathway

Study Interventions

VISA- A Questionnaire - Measuring Pain and Function

The primary outcome measure used in this study was the Victoria Institute of Sports Assessment–Achilles (VISA –A) questionnaire (13). The self- administered questionnaire was completed by all participants who consented to take part in the study. It was completed after the randomisation process but prior to ultrasound scanning of the Achilles tendon which provided a baseline measure of pain and function and again at 12 weeks.

Ultrasound scanning to measure the Achilles tendon thickness and neovascularity

An ultrasound scan was performed, at baseline and at 12 weeks, to measure the tendon thickness (millimetres) and neovascularity (Ohberg score). It was also used at baseline to show any abnormalities in the tendon which might exclude participation in the study. The ultrasound scan was carried out by a consultant radiologist who was a Fellow of the Royal College of Radiologists (FRCR) with 15 years-experience in musculoskeletal diagnostic and interventional ultrasound (one radiologist performed all measurements) using a Logiq E9 (GE Healthcare) ultrasound machine with a GE 9L-D probe. The participant was positioned for the scan in the prone position with their foot freely hanging over the end of the plinth in a neutral position. The ultrasound scan was reported in accordance with Radiology Department protocols and recorded on TRAK (Patient electronic records system). This ensured that the intervention and scan reports were available to ensure continuity of care for any future consultations that might take place out with the study. **Measuring tendon thickness**

The Achilles tendon was scanned in both the transverse and longitudinal axis and a measurement taken of the anteroposterior dimension of the Achilles tendon at the thickened portion. Using the ultrasound machines integrated measurement device the tendon thickness measured in millimetres was recorded for each subject.

Measuring neovascularity.

Power Doppler ultrasound was used to identify and measure neovascularity. It was measured using the Modified Ohberg Neovascularisation Score (Table 5.3).

Table 5.3 Modified Ohberg score for neovascularity (14)

Ohberg's neovascularity Score	Description of neovascularity
0	No vessels visible
1+	One vessel visible mostly anterior to the tendon
2+	One or two vessels visible throughout the tendon
3+	Three vessels throughout the tendon
4+	More than three vessels throughout the tendon

This semi quantitative grading system has been shown to have excellent inter-rater reliability with an Interclass Correlation Coefficient (ICC) of 0.85 (14). The measurement was carried out with the subject in the prone position with the feet positioned at the end of the treatment couch with the ankle in a neutral position. Care was taken to minimise the pressure of the probe on the skin to prevent obliteration of the vessels whilst carrying out the examination. The examination was carried out in the longitudinal and transverse planes.

Control Group – eccentric loading exercise programme

On completion of the ultrasound scan the participants were given an eccentric loading programme by the PI. This included both written and verbal instruction. The information included a demonstration of the exercises along with details on the number of the daily sets and repetitions of each that were required to be performed. Participants were also provided with a diary to record their adherence with the programme by recording the number of sets and repetitions carried out each day for the 12-week duration.

The programme consists of a heel drop exercise carried out from the starting position illustrated in figure 1 A firstly with the knee fully extended (Figure 1B) to eccentrically load the gastrocnemius and then with the knee flexed (Figure 1 C) to eccentrically load the soleus. The programme is based on the Alfredson protocol as first described in 1998 and requires three sets of 15 repetitions of each exercise, carried out twice daily in the morning and evening for 12 weeks. The participants were advised that they should expect to experience some pain whilst performing the exercises.
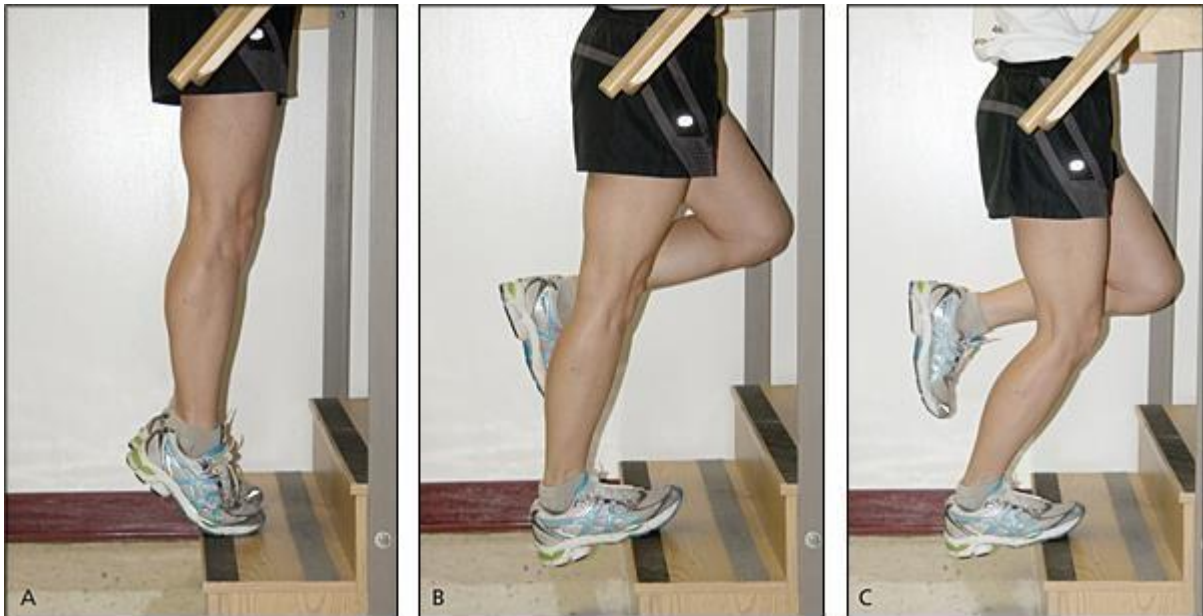
Figure 4 Eccentric loading exercise programme (

Following the completion of the 12-week exercise programme the VISA-A questionnaire was administered and another ultrasound scan to measure tendon thickness and neovascularity. The measurements were reported on TRAK and on the subject's data sheet. The VISA-A score was also recorded.

If at this stage the participants were able to return to their pre-injury levels of activity because of improved levels of function and reduced pain, then they were discharged back to their GP. At this point they were advised that within the following 6 months if they experienced any reoccurrence of symptoms, they could contact the department of orthopaedics and trauma for a follow up appointment without a referral from their GP. If at the 12-week review participants continued to experience pain and had limitations in function which effected their activities of daily living, then they were provided with a follow-up appointment in the department of orthopaedics for continued ongoing care.

Treatment group - HVUGI

For those participants randomised to the treatment group a first ultrasound scan was carried out by the consultant radiologist to measure tendon thickness and neovascularity. Following the first ultrasound scan the participants were asked to remain in the prone position with the knee extended and the ankle in a neutral position. Prior to the administration of the injectable saline, and following cleansing the skin with an alcohol swab, 10ml of 1% lidocaine (local anaesthetic) was administered anterior to the Achilles tendon. The aim of the local anaesthetic was to provide an anaesthetic block and therefore reduce pain during the immediate post-intervention period (1.5 -2.0 hours). Then, under ultrasound guidance and using aseptic techniques, a 21gauge needle attached to a 30cm connecting tube was positioned between the anterior aspect of the Achilles tendon and Kager's fat pad. Under continued ultrasound guidance 40ml of injectable saline was administered targeting the area of neovascularity. On removal of the needle a sterile dressing was applied. This was carried out by the same radiologist who carried out the tendon measurements. On completion   the participants were advised that the area around the Achilles would appear very swollen for about 24-48 hours. They were allowed to

fully weight-bear immediately, with only light activities recommended for 72 hours. After that, participants were encouraged to gradually return to activity.

At 12 weeks the VISA-A questionnaire was administered and an ultrasound scan performed to measure tendon thickness and neovascularity. The ultrasound scan measurements were reported and recorded on TRAK as well as on the subject data sheet. As with those subjects in the control group, if at 12 weeks the participants were able to return to their pre-injury levels of activity because of improved levels of function and reduced pain then they were discharged back to their GP. They were advised that within the following 6 months if they experienced any re-occurrence of symptoms, they could contact the department of orthopaedics and trauma for a follow up appointment without a referral from their GP. If at the 12-week review point participants continued to experience pain and had limitations in function which effected their activities of daily living, then they were provided with a follow-up appointment in the department of orthopaedics for continued ongoing care. **Sample Size**

The sample size of 30 was based on the "rule of thumb sample size estimate" described by (15) Browne (1995). The recruitment period for the study of 6 months. The sample size was considered a suitable size to provide some indication of recruitment rates for a potential future RCT.

Statistical Analysis

All data was analysed using descriptive statistics. As a result of the small sample size any inferential statistics were analysed using nonparametric testing using SPSS version 25 (IBM Corp. Armonk NY)

Results

The primary aims of this study were to evaluate recruitment and retention whilst the secondary aims focused on the experimental phase and analysis of results.

Primary objectives

The study found during 6-month period 63 patients were referred to the department of orthopaedics in a large Scottish Teaching Hospital with Achilles tendon pain. Of those 43 (68%) were considered eligible and 33 (77%) agreed to take part in the study. Of the 33 randomised (treatment group =14, control group 19) two were excluded because of abnormal ultrasound scans. Eight subjects were lost to follow-up at 12 weeks resulting in a retention rate of 74% (n=23). Adherence to the eccentric loading programme was 74% when recording the number of exercise sessions completed as a percentage of the total suggested. No adverse reactions were recorded in those who received the HVUGI with only one subject reporting some discomfort when injecting the saline.

Secondary objectives

The secondary aims in this study would reflect the primary aims of any future RCT and included the use of the VISA-A to measure pain and function, tendon thickness and neovascularity at baseline and at 12 weeks. However, caution regarding the outcome measures should be exercised due to the purposefully small sample size.

		N	Min	Max	Mean (±SD)

Control Group	Baseline VISA-A score	19	8	73	49.58 (17.06)
	Post Intervention VISA -A score	13	16	94	64.00 (25.47)
Treatment Group	Baseline VISA-A score	14	21	85	48.07 (19.78)
	Post Intervention VISA -A score	10	30	98	60.80 (22.75)
Control Group	Baseline – Tendon thickness (mm)	17	6	16	10.41 (± 2.8)
	Post-intervention- Tendon thickness (mm)	13	6	14	9.69 (±7.23)
Treatment Group	Baseline – Tendon thickness (mm)	13	8	14	11.00 (± 2.00)
	Post-Intervention- Tendon thickness (mm)	10	8	15	10.50 (± 2.12)
Control Group	Neovascularity baseline (0-4)	17	0	4	2.12 (± 1.41)
	Neovascularity post-intervention	13	0	4	1.69 (± 1.25)
Treatment Group	Neovascularity baseline	13	1	4	3.31 (± 0.95)
	Neovascularity post-intervention	10	1	4	2.80 (± 1.32)

Table 1 Illustrates the mean, range and standard deviation for the VISA-A scores, tendon thickness (mm) and neovascularity score (0-4) at baseline and post intervention for the control group (Eccentric Loading Exercise programme) and the treatment group (HVUGI).

From Table 1 the baseline VISA-A scores were shown to be similar in both groups with increases in the mean scores post intervention suggesting a reduction in pain and improved function following the administration of a HVUGI or completion of the eccentric loading exercise programme. In the control group the mean VISA-A score increased from 49.58 ± 17.06 to 64.0 ± 25.47 whilst in the treatment group the mean score increased from 48.07 ± 19.78 to 60.80 ± 22.75. In this study the tendon was measured at its thickest point using the inbuilt measuring tool of the Logiq E9 GE Healthcare diagnostic ultrasound machine and GE 9L probe. The results (Table 1) show that the mean thickness of the Achilles tendon at baseline was similar in both groups with a reduction noted in control and treatment groups post

intervention. A reduction in mean tendon thickness from 10.41mm to 9.69mm was found in the control group and in the treatment group a reduction from 11.00mm to 10.50mm. Although a reduction in tendon thickness was noted in both groups, clinically the Achilles tendons still appeared thickened. The score for neovascularity was defined as the number of vessels evident on power doppler ultrasound. The scores were recorded at baseline and post intervention in both the control and treatment groups. The scores range from 0-4 (Ohberg's Score) where 4 is associated with severe tendinopathy and 0 a normal tendon. In the control group the mean neovascularity score reduced from 2.12 ± 1.41 to 1.69 ± 1.25. In the treatment group the mean score reduced from 3.31 ± 0.95 to 2.80 ± 1.32. It is important to note that the mean neovascularity score in the treatment group was higher at baseline than the control group. This variation between the two groups was by chance as the randomisation took place before the ultrasound scanning.

Groups		Difference between baseline and post intervention VISA-A scores	Difference between baseline and post intervention tendon thickness	Difference between baseline and post intervention neovascularity score
Control Group	**p-value**	0.017	0.135	0.442
Treatment Group	**p-value**	0.012	0.705	0.071

Table 2 illustrates the statistical results when comparing the change in the VISA-A scores, tendon thickness and neovascularity scores within the control and treatment groups (sample including missing data)

The Wilcoxon Signed Rank test is the non-parametric equivalent of the paired t-test and allows two sets of scores to be compared from the same participant. By analysing the data in the two groups using this test and a level of significance ≤ 0.05 it was possible to statistically calculate the change in the VISA-A scores, tendon thickness and the neovascularity scores associated with the intervention in the control group (ELE programme) and in the administration of a HVUGI in the treatment group.

The VISA-A scores in Table 2 illustrate a statistically significant difference between the baseline and post intervention scores in both the control group (p= 0.017 and treatment group (p= 0.012). The higher post-intervention scores recorded suggest a clinical improvement (improved function and reduced pain) with both an ELE programme and a HVUGI. No statistically significant change was noted in the tendon thickness or neovascularity between baseline and post intervention in either the control or treatment groups, which suggests tendon thickness and neovascularity are not affected by an increase in the VISA-A score (improved function and reduced pain).

Table 3 illustrates the results of a Mann-Whitney U test to analyse any statistical differences between the control group and treatment group.

	Baseline VISA-A score	Post Intervention VISA -A score	Baseline tendon thickness	Posttreatment tendon thickness	Baseline NS	Post interventi on NS
Mann-Whitney U test	123.000	58.500	91.500	52.500	56.000	34.500
Asymp. Sig. (2-tailed)	0.716	0.687	0.423	0.434	0.018	0.051

The Mann-Whitney U test is a non-parametric equivalent of the unpaired t-test and is used in hypothesis testing although no hypothesis testing was carried out as part of this study due to the small sample size. It was used to compare the dependant variables (VISA-A scores, tendon thickness and neovascularity score) for two independent groups (control and treatment groups).

The analysis illustrated in Table 3 illustrates that there was no significant difference in the VISA-A scores between groups at baseline and post intervention the Mann-Whitney U test used to analyse if there was a significant difference between the control group and treatment group at baseline and post intervention. Similarly, there was no statistically significant difference noted for tendon thickness between the treatment group and control group both at baseline and post intervention. However, with regards to the neovascularity score there was a significant difference between the groups at baseline, with NS scores higher in the treatment group. Post-treatment the results marginally suggest no difference in the NS (p=0.051). A review of the descriptive statistics suggest that the percentage change was similar in both the control and treatment groups. **Discussion**

To our knowledge this is the first study to investigate the feasibility of carrying out an RCT to compare HVUGI with eccentric loading exercises for the management of non-insertional Achilles tendinopathy.

Recruitment

The proposed plan was to recruit 30 participants in a four-month period. . As no funding was available the study was conducted within the confines of normal service delivery with the agreement that 1 clinical session per week (3 hours) would be protected for the Principle Investigator (PI) and Consultant Radiologist to conduct the study. This was formally agreed as part of their work plans and was coordinated to ensure that there was adequate clinical space available including diagnostic ultrasound equipment. In planning the resource allocation, it was

important to include both the recruitment period and the review period, which for this study extended to approximately seven months (4-month recruitment plus 12 week follow up). It was estimated that that within the given three-hour period a maximum of three participants could consent, be randomised, undergo an ultrasound scan and receive the treatment intervention. At the 12-week point if the recruitment target had not been reached the clinical session could be a mix of new participants and 12-week reviews with the intent of reaching the target sample of 30 whilst reviewing participants in accordance with the agreed protocol. As a consequence of staff shortages and increased waiting times the availability of the Consultant Radiologist was reduced to just one hour per week (between 8am and 9am). Therefore, recruitment was reduced to one new participant per week (instead of three) or two reviews. The reduction in recruitment capacity required an extension to the study period to 10 months (6 months recruitment plus 4 months for the 12-week reviews). Within this revised study period the target sample of 30 (n=33) was achieved. This sample was drawn from 43 patients assessed as eligible of which 10 (22%) declined to take part due to scheduling and travel issues. The approximate recruitment rate achieved by the feasibility study was 1.3 participants week compared with the originally planned rate of 1.7 participants per week. **Eligibility**

The eligibility rate was defined as the number of eligible subjects as a proportion of the total screened patients. During the six-month recruitment period 63 patients were referred to the department of orthopaedics with Achilles tendon pain and screened for eligibility. Of those, 20 were excluded due to fulfilling exclusion criteria which included receiving previous treatment (n=8), bilateral presentation (n=7) and a diagnosis of insertional Achilles tendinopathy (n=5). Therefore 43 subjects were eligible for enrolment into the study equating to an eligibility rate of 68%. This eligibility rate was directly affected by the recruitment process which relied on triaging of patients referred to the department of orthopaedics and the information provided on the referral letter. This information was often vague and as such important exclusion criteria were not identified resulting in 32% of screened patients being excluded.

Retention/ Attrition

Of the 31 subjects that entered our study (18 in the control group and 13 in the treatment group), eight subjects were lost to follow-up equating to 26% attrition. One subject voluntarily withdrew within two weeks of being recruited. Three failed to respond to follow-up appointment requests and four stated that they could not make the early morning review appointment imposed because of the reduced availability of the Consultant Radiologist.

Attrition is a key consideration when designing an RCT and was quantitatively reported as a primary aim in this study. The attrition rate was calculated to inform the sample size estimate for a future RCT. If attrition is not taken into consideration, then there is a possibility that the RCT could be underpowered and raise the issue of type II bias. The loss of subjects to followup can also introduce bias by altering the characteristics between the randomised groups (16), whilst leaving some questions unanswered about the intervention and any adverse reaction if subjects are lost to follow-up.

It has been suggested that where attrition is greater than 20% there is concern about the possibility of bias (17). Therefore, an understanding of why subjects were lost to follow-up in our study is imperative for future planning. The aim would be to reduce attrition to below a 20% threshold in any future RCT.

Adherence with Eccentric Loading Exercise Programme

In this study adherence with the exercise programme was evaluated with the use of an adherence diary which the participants randomised to the control group were asked to complete each day across the 12 weeks. Participants in our study were asked to record if they completed the exercises and how many sets and repetitions in each session. By doing this it was possible to record the frequency (number of sessions per week) and the intensity (number of repetitions per session). Mean adherence was measured as the number of sessions completed as a percentage of the total. A session was considered completed if the participant performed three sets of each exercise even if they were unable to manage the full 15 repetitions. Return rate for the diaries was 69%. Mean adherence was calculated at 74% (Minimum 58.3% Maximum 99.4%).

The eccentric loading exercise programme used in this study is long, laborious, and often painful to do. Painful exercises are not necessarily intuitive to perform and therefore adherence with such a programme is important to establish. It has been reported that poor adherence to unsupervised home-based exercise programmes could result in the programme being considered ineffective rather than a result of insufficient regime effect (18), whilst self-reporting can lead to both under and over-estimation of how much exercise a patient might perform (19). In addition, an individual's beliefs and attitudes can also influence adherence to an exercise programme. From a pragmatic perspective, if adherence to a programme with the characteristics described by Alfredson (1998) is poor then its value as a therapeutic intervention might well be questioned and responsible for the variable results

Earlier studies set the minimum adherence threshold at greater than or equal to 75% for similar eccentric loading exercise programmes. (20, 21) with one achieving an adherence rate of 81 $\pm$ 7% whilst the other reported a decline in adherence over the duration of the programme, peaking at 80% at weeks 2-7 before declining to 50% in week 13.

If 75% is considered the threshold for satisfactory adherence, then adherence in our feasibility fell just short at 74%. Therefore, some method of improving adherence might be considered for a future RCT. Text messaging is used extensively in all areas of healthcare to remind patients of appointment times or when they are due review appointments or health checks. It has been suggested that text messaging programmes (SMS) on mobile phones can help people change health behaviours and has been used in medication adherence, smoking cessation, diabetes management and weight loss (22). Text messages are usually sent by automated systems and are likely to be read within minutes of being received in contrast to information sent in the post. In addition to changing health behaviours, it has been shown to improve compliance with home-based exercise programmes. An RCT found that an intervention group which received regular text messaging every day for two weeks reported higher compliance than a control group, which, translated into improved function (23).

The results pertaining to adherence in this study should be viewed with caution because of the small number of returned diaries from a small sample size. Although we are unable to establish with any confidence the overall adherence rate to the eccentric loading exercise programme in this study, from the data analysed it would seem low and with an exercise programme with such a long duration (12 weeks) it would seem prudent to provide some method of reminding / encouraging participants in a future RCT. Therefore, the intention would be to continue with the adherence diaries for participants to complete, whilst providing text messaging at 2-week intervals in any future study.

Adverse reaction

Of the 14 subjects who received the HVUGI no adverse reactions were recorded during or postinjection. One subject reported that the administration of the saline around the tendon was uncomfortable and asked that the consultant radiologist stop the procedure before administering the full 40ml. The subject reported that it made them feel a "little nauseous" however this subsided as soon as the administration of the saline was suspended. This subject was followed up 24 hours later and they reported no lasting adverse effects to the treatment.

Randomisation

The randomisation was performed using an online randomisation programme (Sealed Envelope). This system is tried and tested and has been used extensively by Higher Education institutions both in the UK and abroad, NHS Boards as well as the MRC Trials Unit.

The aim of randomising the participants was to achieve similarity of baseline characteristics in both groups. Failure to do this can result in different baseline characteristics which can have confounding effects on the outcome of the study thus challenging what effect the intervention had on both the Patient Reported Outcome Measures (PROMs) and other physical characteristics measured (24). Confounding factors can include issues around demographics, such as age and gender, as well as prognostic factors and those characteristics which may influence participation and compliance. In addition to ensuring baseline characteristics, randomisation should also ensure a balance of numbers between groups. Block randomisation was used in this study to allocate patients to the two groups. Block sizes of four, six and eight were used. The decision to use random block sizes were to reduce the predictability and possible selection bias that can occur when using a single block size (25). The randomisation process allocated 33 participants to either to either the control or treatment arm of the study with a total of 34 randomisations carried out (1 trial randomisation was performed at the start of the study).

An imbalance in the numbers allocated to each arm of the trial was seen, with the process randomising 19 participants to the control group and 14 to the trial group. One explanation was the setting of the sample size to 50 with Sealed Envelope rather than reducing it to reflect the proposed sample size of thirty. This combined with the randomised block sizes of 4, 6, and 8 could be responsible for the discrepancy in the group sizes after carrying out 34 randomisations. However, some have challenged the idea that randomised trials need to yield equal groups and even suggested that this can lead to bias by reducing the unpredictability of the assignment of subjects to treatment groups (17). Therefore, in the context of this study the unequal numbers in each arm were acceptable and the use of block randomisation in a future study should be monitored carefully.

The intention for a future trial would be to use the online randomisation programme (sealed envelope). The general process of randomisation using this online programme was simple and easy to use. The imbalance experienced in this study, although considered acceptable, might be addressed by setting the sample size to the target sample size rather than overestimating. Regular monitoring of the balance across the groups would be carried out to ensure that the sample size in each arm were similar.

Secondary outcome measures

In reviewing these results, it is important to note that the analysis of data in this study was primarily to trial the methods that might be used in a future RCT and that any results should be viewed with caution because of the purposefully small sample size.

Evaluating pain and function using VISA –A questionnaire

The mean baseline VISA-A scores were similar in the control and treatment groups. Both groups lost subjects to follow-up. Each group showed an increase in the mean VISA- A score with the control group mean score increasing by 14.42 points from a baseline score of 49.58 ± 17.06 whilst the treatment group increased by 12.73 from a baseline score of 48.07 ± 19.78. Using a Wilcoxan Signed Rank Test there was a statistically significant improvement, which was also clinically significant. However, there was no significant difference in the VISA-A scores between the control and treatment groups at baseline or at 12 weeks.

Tendon Thickness

One of the key diagnostic features of non-insertional Achilles tendinopathy is evidence of thickening about 2-6cm from the insertion of the tendon into the calcaneus. The tendon either side of this thickened portion has a normal appearance on ultrasound examination, and it is the thickened portion that is referred to when studies on non-insertional Achilles tendinopathy report tendon thickness. In this feasibility study the tendon thickness was measured at baseline and at 12 weeks. The mean tendon thickness reduced from 10.41mm $\pm$ 2.8mm to 9.69mm $\pm$ 7.23mm in the control group whilst in the treatment group tendon thickness reduced from 11.00mm $\pm$ 2.00mm to 10.50mm $\pm$ 2.12. While the reported means show some minor changes, clinically the tendons at 12 weeks still appeared thickened in the midportion area compared to the proximal and distal portions and was difficult to see during physical examination. Statistical analysis of the mean values using a Wilcoxon Signed Rank Test showed there was no statistically significant change in the tendon thickness because of the HVUGI (treatment group) or the eccentric loading exercise plan (control group) when measured at 12 weeks in addition, using a level of significance of ≤ 0.05 a Mann-Whitney U Test showed no statistical difference in the tendon thickness between the control group and the trial group at both baseline and at 12 weeks. The reduction in tendon thickness is supported by other studies which have evaluated HVUGI (26,27,28) however it is difficult to draw direct comparisons due to the time interval for evaluation and different injection regimes. What these other studies did report was that clinically the tendon still appeared thickened even if the mean measurement reduced.

Neovascularity

Neurovascular ingrowths, alongside thickening of the Achilles tendon are key diagnostic features of non-insertional Achilles tendinopathy. In our study 90% of subjects (n=28) showed evidence of neovascularity when examined at baseline. This compares with 66% of tendons exhibiting neovascularity in one study (29), whilst another study 30by Zanetti et al., (2003) found evidence of neovascularity in 30 of 55 symptomatic tendons (55%) but only in one of 25 asymptomatic (4%) tendons (30). These are contrary to the results from other authors who found that all patients in their study (41 tendons in 30 patients) exhibited neovascularity when examined with Doppler ultrasound. Following a 12-week eccentric loading exercise plan and

at a mean follow-up of 28 months, 36 of the 40 tendons (90%) were asymptomatic with no pain reported during activity. Of those 36 tendons, 32 did not show any signs of neovascularity (89%) (31).This contrasts with our study which found no relationship between neovascularity and the VISA-A score. The mean neovascularity score did reduce between baseline and 12 weeks although 21 of the 23 (91%) tendons still exhibited neovascularity. However, it should be noted that the mean follow-up was significantly longer, than the 12-week post intervention follow-up in our study and therefore the rehabilitation process would be more complete.

Conclusion

This study identified some key issues which could challenge the feasibility of carrying out a future RCT. This included issues around recruitment, retention, and adherence to the eccentric loading exercise programme. It was also seen that this study failed to assess any early improvements in function and reduction in pain when comparing the control and treatment group which should be addressed in any future study. Therefore, it is suggested that a pilot study is carried out with modifications made to improve areas of deficit and implement changes which include earlier evaluation of pain and function. Only if these areas show improvement to an agreed threshold should a future RCT be considered.

Supplementary Information

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Authors Contribution

JV conceived and designed the study. JV led the data analysis and interpretation and writing of the study report. JD and TR contributed to the study design, data analysis and interpretation of the results. JF contributed to the development of the protocol developed for the administration of the HVUGI

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Availability of data and materials

The data used in this study is available are available from JV on reasonable request.

Competing Interests

The authors declare that they do not have any competing interests.

Ethical Approval and consent to participate

Ethical approval was granted by Southeast Scotland REC (REC no 17/55/0107). Written consent was obtained from all participants in the study.

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