Haemarthrosis of the ankle in haemophilia A and B: prevalence, impact and intervention

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Submitted in accordance with the requirements for the degree of Doctor of Philosophy

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The University of Leeds

May 2021

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Acknowledgements

The course of a five year PhD is a long one and across the journey, there is a long list of people who have listened, advised and supported me. I would firstly like to thank my supervisors Professor Anthony Redmond and Associate Professor Heidi Siddle who have driven me towards a clinical academic career. Both Anthony and Heidi have invested time and expertise in the development, implementation and delivery of this PhD as well as championing my career to date. I will be eternally grateful for all of their support past, present and future.

I would also like to thank Dr Graham Chapman and Dr Rebecca Walwyn who have provided supervision and guidance throughout my PhD. Dr Lishel Horn is also thanked.

I would like to thank the National Institute for Health Research who funded this body of work, and the clinical training that has been gained throughout my Clinical Doctoral Research Fellowship (ICA-CDRF-2015-01-012).

Leeds Teaching Hospitals NHS Trust who have supported this PhD, with specific mention to the Podiatry manager Thomas Dickie who has been very understanding and accommodative throughout.

I would also like to thank the following:

- Members within the Leeds Institute of Rheumatic and Musculoskeletal Medicine, section of clinical biomechanics and physical medicine research group Lara Chapman, Dr Begonya Althea Pritchard and Professor Anne Maree Keenan.
- Dr David Lunn for his assistance and support both academic and personal
- Dr Jill Halstead for her personal support and advice.
- Lee Short and Bob Longworth, both of whom have supported the development and clinical application of this PhD.
- Professor Cathy Bowen who provided support as my NIHR mentor.
- Dr David Stephensen for his guidance specific to haemophilia, his assistance in the prevalence chapter and links that allowed recruitment at haemophilia centres across the United Kingdom.
- The Haemophilia Chartered Physiotherapists Association, the United Kingdom Haemophilia Doctors Organisation and National Haemophilia Database.

I would like to thank my wife Rebecca Wilkins for her unwavering patience, understanding, support and our two beautiful children Matilda and Sebastian both of whom were born during this PhD.

Co-author contribution

This research has been undertaken by a team with my contribution and other author contributions explicitly indicated below:

Chapter Three - *The prevalence of ankle haemarthrosis in moderate and severe haemophilia A and B*

The concept and design were conceived by RAW, AR, HS and DS. Data were collated and analysed by the NHD with DS and RAW. All authors (RAW, AR, HS, GC, LH, DS, and RW) contributed to the analysis and interpretation of data. RAW drafted the chapter and all authors revised the chapter. RAW takes responsibility for the integrity of the work as a whole from inception to the finished chapter.

Chapter Four - *The impact of blood induced ankle arthritis in patients with moderate and severe haemophilia A and B: The HAPII study*

The concept and design were conceived by RAW, AR, and HS. RAW collected and assembled the data with statistical support from RW and AR. All authors (RAW, AR, HS, GC, LH, DS, and RW) analysed and interpreted data. RAW drafted the chapter with statistical support from RW and all other authors (AR, HS, GC, LH, and RW) revised the chapter for content. RAW takes responsibility for the integrity of the work as a whole from inception to the finished chapter.

Chapter Five - *A mechanism of action study to explore the individual and combined components of the Leeds Ankle Stabilising Enhanced Rocker (LASER) Boot*

The concept and design were conceived by RAW, AR, and GC. RAW collected and assembled the data with technical and statistical support from GC, AR and RW. Authors (RAW, AR, HS, GC, and RW) analysed and interpreted data. RAW drafted the chapter with statistical support from RW and all other authors (AR, HS, GC, DS, and RW) revised the chapter for content. RAW takes responsibility for the integrity of the work as a whole from inception to the finished chapter.

List of publications/ presentations arising from this thesis

Original articles

Conference and oral presentations

Wilkins RA. “Haemarthrosis of the ankle in moderate and severe haemophilia, prevalence, impact and intervention; the HAPII study” Scottish Inherited Bleeding Disorders Network (SIBDN), November 2020

Wilkins RA, “Haemarthrosis of the ankle in moderate and severe haemophilia, prevalence, impact and intervention; the HAPII study**”** 13th Annual Congress of the European Association for Haemophilia and Allied Disorders, The Hague, February 2020

Wilkins RA, “Ankle haemarthrosis and haemarthropathy primary data from the HAPII study” Invited Speaker**,** United Kingdom Haemophilia Doctors Centres Organisation, November 2019

Wilkins RA, Haemarthrosis of the ankle in haemophilia A and B; prevalence impact and intervention**,** M62 Corridor Haemophilia education meeting, May 2018

Wilkins RA, Ankle pathology in haemophilia, OSGO live national podiatry private practice conference, UK October 2017

Wilkins RA, Haemophilia in Children, Podo-paediatric podiatry conference, UK 1st July 2016

Wilkins RA, Longworth R The use of footwear and orthoses in the management of bleeding disorders, Northern haemophilia physiotherapy meeting, UK May 2016

Conference poster presentation

Wilkins RA, "Haemarthrosis of the ankle in moderate and severe haemophilia, Prevalence, impact and intervention; the HAPII study**".** February 2020, Poster presentation, 13th Annual Congress of the European Association for Haemophilia and Allied Disorders, The Hague

Richard A Wilkins**, "**Haemarthrosis of the ankle in moderate and severe haemophilia, Prevalence, impact and intervention; the HAPII study**".** February 2020, Poster presentation, 13th Annual Congress of the European Association for Haemophilia and Allied Disorders, The Hague

Wilkins, R.A., Siddle, H.J., Palmer, B., Chapman, G.J., Scott, M., Xiang, H., Walwyn, R., Richards, M., Horn, L., Redmond, A.C. and Stephensen, D., 2020, February. Prevalence of haemarthrosis and clinical impact on the musculoskeletal system in people with haemophilia in the United Kingdom; evaluation of UKHCDO and haemtrack patient reported data. In *haemophilia* (vol. 26, pp. 116-117). 111 river st, Hoboken 07030-5774, nj usa: Wiley.

Wilkins, R.A., Siddle, H.J., Chapman, G.J., Horn, L., Walwyn, R. and Redmond, A.C., 2020, February. The impact of ankle haemarthrosis on moderate and severe haemophilia a and b the HAPII impact study. In *haemophilia* (vol. 26, pp. 115-116). 111 river st, Hoboken 07030-5774, nj usa: Wiley.

Talbott, H., **Wilkins, R**., Redmond, A., Brockett, C. and Mengoni, M., 2020, February. The influence of subchondral bone cysts on tissue pressures in the tibiotalar joint. In *haemophilia* (vol. 26, pp. 33-33). 111 river st, Hoboken 07030-5774, NJ usa: Wiley.

Wilkins, R.A., Siddle, H.J., Chapman, G., Redmond, A.J., Xiang, H., Scott, M., Richards, M., Horn, L., Palmer, B. and Stephensen, D., 2020. P107 Prevalence of haemarthrosis and clinical impact on the musculoskeletal system in people with haemophilia in the United Kingdom: evaluation of UKHCDO and haemtrack patient reported data. Rheumatology, 59 (Supplement_2), pp.keaa111-105.

Abstract

Haemophilia is an X-linked recessive genetic disorder characterised by bleeding within soft tissue and joints. Multi-joint disease is a common feature of severe haemophilia where the ankle is prone to haemarthrosis and haemarthropathy, but little is known about the effect on individual joints, impact on health-related quality of life (HRQoL) and foot and ankle outcome measures.

A multi-methods approach was used to improve the understanding of ankle haemarthrosis and resultant haemarthropathy. The prevalence of ankle haemarthrosis and incidence at individual joints with concurrent joint health in patients compliant with prophylaxis without an active inhibitor were investigated. Approximately 60% and 40% of people with haemophilia A and B respectively experienced a minimum of one haemarthrosis over the 12 month study period. Whilst haemarthrosis incidence at individual joints was similar, the ankle was the most affected by haemarthropathy. A multi-centre patient questionnaire of the impact of ankle haemarthrosis and haemarthropathy identified that HRQoL and foot and ankle outcome measures were poor regardless of haemophilia type, severity or treatment regime. A consultant survey identified adequate access to Musculoskeletal (MSK) services across the UK. However, only 12% and 49% of patients used footwear and foot orthoses respectively. Finally, a biomechanical study was established in a healthy cohort of males, the kinetic and kinematic effect of the Leeds Ankle Stabilising Enhanced Rocker intervention, a footwear and foot orthoses intervention used clinically in the management of haemophilia. Significant reductions in the primary outcome of ankle moment of force were reported when compared to a trainer, with a minimal effect on proximal joints.

The work presented in this thesis improves the understanding of the current prevalence, incidence and impact of ankle haemarthrosis and haemarthropathy. Gaps in the access to MSK services have been identified and the mechanism of action of a targeted intervention has been established, providing a basis for future research in a pathological cohort with ankle haemarthropathy.

Richard A Wilkins
May 2021

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List of abbreviations

ABR	Annual Bleed Rate
ADL	Activates of daily living
AFO	Ankle-foot orthoses
AHP	Allied health professional
AJBR	Annual Joint Bleed Rate
AMTI	Advanced Mechanical Technology Incorporated
AOFAS	American Orthopaedic foot and ankle society
BM	Boot mounted
BMD	Bone mineral density
BMI	Body mass index
CAH	Chapel Allerton Hospital
CAST	Calibrated anatomical system technique
CCC	Comprehensive care centre
CFC	Clotting factor concentrates
CI	Chief investigator
CMC	Coefficient of multiple correlation
CoP	Centre of Pressure
DF	Degrees of freedom
EHL	Extended Half Life
EVA	Ethylene-vinyl acetate
FE	Finite element
FFI	Foot function index
FFO	Functional Foot Orthoses
FIX	Factor nine
FM	Foot mounted
FPI	Foot posture index
FVIII	Factor eight
GP	General practitioner
GRF	Ground reaction force
HC	Haemophilia centre
Haemo-QoI	Haemophilia quality of life
HAEMO-QoI-A	Haemophilia quality of life in Adults
HAL	Haemophilia activities list
HC	Haemophilia treatment centre
HEAD US	Haemophilia early detection of joint Disease
HIV	Human immunodeficiency virus
HJHS	Haemophilia joint health score
HRA	Health Research Authority
HRQoL	Health Related Quality of Life
IA	Intra-articular
IC	Initial contact
ICC	Intra class correlation
ICF	International classification of functioning, disability and known health
IL	Interleukin
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IQR	Inter quartile range
IRAS	Integrated Research Application System
ISTH	International Society on Thrombosis and Haemostasis
LASER	Leeds Ankle Stabilising Enhanced Rocker
LC	Lara Chapman
MOXFQ	Manchester Oxford Foot Questionnaire (foot and ankle)
MRI	Magnetic resonance imaging

MS	Midstance
MSK	Musculoskeletal
MTP	Metatarsal phalangeal
NHD	National Haemophilia Database
NHS	National health service
NIHR	National Institute for Health Research
NPRS	Numerical pain rating scale
OA	Osteoarthritis
OFM	Oxford Foot Model
PI	Principle investigator
PIS	Patient information sheet
PK	Pharmacokinetic
POCUS	Point of care ultrasound
PRICE	Protection, Rest, Ice, Compression, Elevation
PROM	Patient reported outcome measure
PRP	Platelet rich plasma
QoL	Quality of Life
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
REML	Restricted maximum likelihood
RMSE	Root mean square error
ROM	Range of motion
SACH	Solid ankle cushioned heel
SAS	Statistical analysis software
SD	Standard deviation
SE	Standard error
SF-36	36-Item Short Form Survey
SHL	Standard Half Life
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for the Social Sciences
ST	Subtalar
TAR	Total ankle replacement
TC	Talocural
TO	Toe off
TNF	Tumour necrosis factor
UK	United Kingdom
UKHCDO	United Kingdom Haemophilia Centres Doctors Organisation
US	Ultrasound
USA	United States of America
VAS	Visual analogue scale
VIIIa	Activated Factor eight
WFH	World Federation Haemophilia
WHO	World Health Organisation
3D	Three-dimensional

Chapter 1 - Introduction

This review provides a description of haemophilia, a detailed review of the biological and mechanical drivers of haemarthrosis; the effect of intra-articular bleeding on structures and function, with particular focus on the foot and ankle; and the final section reviews in detail current treatment modalities of ankle haemarthrosis and haemarthropathy outside of replacement factor concentrate haemostasis.

1.1 Background

Haemophilia, an X-linked recessive genetic disorder is characterised by bleeding within soft tissue and joints [1]. Severe and moderate levels of haemophilia A and B are associated with multi-joint haemarthropathy whereby haemarthrosis and the process of the removal of blood products lead to synovitis, cartilage damage and eventual bony joint changes with loss of joint structure and function. The replacement of Factor VIII and IX with clotting factor concentrates (CFC) treatment has revolutionised haemophilia care with reductions in annual bleed rates (ABR) and annual joint bleed rates (AJBR) [2]. However, despite adequate availability of CFC in western medicine, treatment is still regarded as sub-optimal with low treatment doses ABR and AJBR are still regarded as high [3-5].

The consequence of bleeding is reflected in the levels of haemarthropathy at the most affected joints, the elbows knees and ankles. Until the introduction of prophylaxis, the knee was the most affected by haemarthropathy, however, the ankle has become the most affected joint [6, 7]. In adults, ankle joint changes are reported in the second and third decade of life with a gradual change in joint structure and function leading to gradual plantarflexion deformity and loss of ankle sagittal plane range of motion of up to 80% [8].

The ankle joint has been identified as the most common site of haemarthrosis but little has been reported on prevalence and incidence at an individual joint level, or the impact

on health-related quality of life (HRQoL) and foot and ankle outcomes [9]. Footwear and orthoses have the potential to reduce pain, AJBR and lessen the burden of disease, but there is yet to be any definitive trial that informs clinical management guidelines.

The ankle joint is problematic in the management of pain and haemarthropathy with the suggestion that the ankle may disproportionality affect HRQoL and the burden of disease compared to the other commonly affected joints. [10, 11]. It remains unclear as to the true impact of ankle haemarthropathy and the effect of haemophilia type, severity and treatments regimes.

Access to musculoskeletal (MSK) services for the management of haemarthropathy forms part of the United Kingdom Haemophilia Centres Doctors Organisation standards of care including services such as orthopaedics, diagnostic imaging services and physiotherapy [12, 13]. Podiatry services reported at two United Kingdom haemophilia centres (Leeds and Kent) provide services as part of the clinical comprehensive care model with good patient satisfaction [14]. Improvements in pain, HRQoL and reductions in AJBR are reported when orthoses and footwear are provided, but there is yet to be any national recommendation on use. It is unclear if this service is provided nationally, or if there are disparities in the provision of MSK services [15, 16].

In diseases that affect the foot and ankle such as rheumatoid arthritis and diabetes, there is good evidence that functional foot orthoses (FFO) and footwear prevent foot deformity, provide stability and improve patient-reported outcome measures [17-20]. However in haemophilia and ankle haemarthropathy the evidence is less conclusive, limited to small studies and often used as an adjunct to other therapies [8, 21-25].

The Leeds comprehensive care centre has used FFO and a modified military boot for a decade to manage ankle haemarthrosis, haemarthropathy and reduce patient-reported pain and disability [15]. Whilst audit data has identified improvements in pain and foot and ankle outcomes, little is known about the mechanical effect of the Leeds Ankle

Stabilising Enhanced Rocker (LASER) intervention at the ankle and the proximal joints of the lower limb.

1.2 Thesis hypothesis, and objectives

The two linked hypotheses explored in this thesis are:

- **The prevalence and incidence of haemarthrosis disproportionately affects ankle joint health and the impact of ankle haemarthropathy is a major contributor to the decline in health-related quality of life and foot and ankle outcomes**

- **Improving the understanding of the mechanics of footwear modification and foot orthoses will lead to better targeted non-pharmacological interventions in the management of ankle haemarthropathy**

Objectives

- Establish the current prevalence and incidence of haemarthrosis in adults with severe and moderate haemophilia and concurrent joint health

- To understand the impact of haemarthropathy on HRQoL and foot and ankle outcomes

- Investigate current access to clinical services at comprehensive care and haemophilia treatment centres

- Understand patient perceptions of access to clinical services

- To understand the mechanical effect of the LASER intervention on individual and combined footwear components as a potential non-pharmacological treatment in ankle haemarthropathy

1.3 Thesis structure and overview

Chapter Two - ***Narrative literature review***

This narrative literature review presents the current background and treatment of haemophilia with themes of prevalence of haemophilia, structural and functional consequences of ankle haemarthropathy providing context to this thesis.

Chapter Three - ***The prevalence of ankle haemarthrosis in moderate and severe haemophilia A and B***

This prevalence chapter uses data provided by the national haemophilia database to determine the current prevalence of ankle haemarthrosis and other commonly affected joints of the knees and elbows in adults with moderate and severe haemophilia.

Chapter Four - *The impact of blood induced ankle arthritis in patients with moderate and severe haemophilia A and B: The HAPII study*

The impact of blood induced ankle arthritis has been investigated in this chapter with a specific focus on the impact on HRQoL and foot and ankle outcomes. Details of effect at other joints, pain, treatment and management were collected and compared across haemophilia type, severity and treatment regime.

Chapter Five - *A mechanism of action study to explore the individual and combined components of the Leeds Ankle Stabilising Enhanced Rocker (LASER) Boot*

A mechanism of action study was undertaken to determine the kinetic and kinematic effect of the Leeds Ankle Stabilising Enhanced Rocker intervention in terms of the individual and combined components. This chapter used a group of healthy controls to determine the kinetic and kinematic effects of the LASER intervention and improve understanding of the proposed clinical effect. Findings from this chapter aim to inform a future study of the LASER intervention in those affected with ankle haemarthropathy.

Chapter Six - ***Discussion, future direction and conclusions***

This chapter discusses the main finding of the thesis, the future direction of research and a conclusion on the overall body of work. Future directions for research are discussed and an overall conclusion is drawn.

Chapter 2 - Literature review

This review provides a description of haemophilia, a detailed review of the biological and mechanical drivers of haemarthrosis; the effect of intra-articular bleeding on structures and function, with particular focus on the foot and ankle; and the final section reviews in detail current treatment modalities of ankle haemarthrosis and haemarthropathy outside of replacement factor concentrate haemostasis.

2.1 Haemophilia

This section describes haemophilia, current treatment approaches and complications and the pathogenesis of haemarthropathy with a specific focus on ankle joint haemarthropathy.

Haemophilia is a rare X-linked recessive genetic disorder characterised by bleeding into soft tissue and joints whereby there is an absence, reduction or dysfunction of circulating clotting factor needed to maintain haemostasis [1]. The most common types of haemophilia are A and B, an absence of clotting factor VIII and IX, respectively. Haemophilia is further characterised as mild (>0.05 - <0.24 IU/mL), moderate (0.01-0.05 IU/mL) or severe (<0.01 IU/mL) dependant of the level of clotting factor absence [26]. The global prevalence of haemophilia A and B is approximately 1:5000 and 1:30000, respectively, regardless of ethnicity or descent [27, 28]. Diagnosis of haemophilia occurs because of known family history or at the presentation of bleeding. Most children are symptom-free until they start learning to crawl and walk when the risk of spontaneous and traumatic bleeding is increased [1]. Severe haemophiliacs are most at risk of spontaneous bleeding events while those with moderate disease often bleed because of trauma. However recent focus has been placed on moderate haemophilia where patients who have a tendency to bleed or have a “bleeding phenotype” require regular clotting factor concentrate (CFC) treatment [4, 29]. The treatment of severe and moderate (bleeding phenotype) haemophilia is by the replacement of clotting factors termed

‘replacement therapy’ to elevate a patient’s trough level (FVIII/ FIX) to a level adequate for stopping or minimising spontaneous bleeding events and subsequent joint damage [30, 31]. Nilsson *et al.* (1970) observed that children with moderate haemophilia did not display the same tendency for episodes of acute spontaneous bleeding as those with severe disease. Therefore elevation of trough levels above 1% (>0.01 IU/mL) by regular infusion of anti-haemophilia concentrate termed prophylaxis treatment may minimise spontaneous bleeds [32]. Longitudinal studies of prophylaxis verses episodic on-demand treatment have reported successful reduction of haemarthrosis and structural joint damage [33-36].

Episodic on-demand treatment whereby CFC is administered after a bleed, or at the patients chosen time such as before physical activities, is often adopted in socially economically deprived countries [1]. In the United Kingdom (UK), the numbers of patients who treat on-demand have declined dramatically since the introduction of prophylaxis. Nearly all children (94%) and 74% of older adults aged 30 years and above with severe haemophilia A are now adopting a prophylaxis treatment regime [2]. On-demand treatment is associated with a higher risk of complications, long-term disability caused by intra-cranial haemorrhage and high incidence of joint damage, disability and reduced life expectancy [11, 37]. A proportion of adult patients still choose to treat on-demand, due to a lack of treatment compliance, infusion difficulties or mistrust of treatments [4, 38]. In adults where treatment was either unavailable in early years or a preference for on-demand treatment, secondary prophylaxis is often adopted in later years [30]. Collins *et al.* (2011) examined the efficacy and safety of secondary prophylaxis in adults with severe haemophilia A (n=19). In this crossover study, patients were observed over a six month period treating on-demand with CFC. Over the following six months patients received prophylaxis with standard half-life (SHL) CFC of 20-40 IU kg^{-1} three times per week [2]. Results identified that when adhering to a prophylaxis treatment regimen, the cohort reduced episodes of bleeding and haemarthrosis from a median of 15.0 (IQR 11 to 16) to 0 (IQR 0 to 3) (P=<0.001) [2]. Results provide evidence of the effectiveness of

prophylaxis even where joint disease is established. Findings made little difference to joint health and the reduction of pain with mean (standard deviation) visual analog scales (VAS) of 3.7 (SD 2.9) to 3.3 (SD 3.0) over the 13 month study period was not significant. Quality of life (QoL) was not affected by treatment, though little detail was provided on total HEAMO-QoL-A or domains scores which may have provided more insight to effect [2].

2.1.1 Anti-factor antibodies

Whilst prophylaxis has revolutionised haemophilia treatment it is not without complication. Inhibitor development whereby anti-Factor antibodies are produced in response to the infusion of CFC triggers an immune response that inhibits the effect of CFC treatment [39]. The incidence for inhibitor development is higher in haemophilia A than haemophilia B. Development of anti-Factor VIII (FVIII) antibodies occurs in 30%, and anti-Factor IX (FIX) antibodies occur in 3% of previously untreated patients, with risk of inhibitor development observed in the first 20-30 days or 20-100 treatment exposures [1, 39, 40]. The development of inhibitors can be catastrophic if not identified, with treatment essentially ineffective. Where bleeding continues, restoration of haemostasis requires the use of bypassing agents such as activated prothrombin complex concentrates, recombinant factor VIIIa and more recently recombinant, humanized, bispecific monoclonal antibodies [41, 42]. Hanley *et al.* (2017) indicate that the frequency of spontaneous joint and soft tissue bleeds in patients with inhibitors are comparable to non-inhibitor cases, but inhibitor cases have a higher tendency to develop “target joints”, i.e. a joint that is particularly prone to bleeding [43]. A target joint is defined as a joint that has had three or more haemarthrosis episodes within a six month period resulting in joint synovitis and increased risk of repeated haemarthrosis, an indicator of under treatment [44, 45].

2.1.2 Haemarthrosis

Haemarthrosis, whereby single significant or repeated episodes of bleeding occurs with a joint space is an inherent clinical feature of haemophilia [46]. The presence of blood within the joint space and the process of removal is associated with synovial hypertrophy, haemosiderin deposition and eventual arthropathic changes to joint structure [23]. A single traumatic episode of bleeding into a joint can lead to a biological cascade that causes joint damage and disability (Figure 1). This is a particular concern in children where musculoskeletal immaturity exposes joints to a greater risk of damage and rapid decline in joint health if haemarthrosis is not prevented [3].

One large European study of haemophilia reported high annual bleed rates (ABR) across multiple countries [3]. The study identified patients with severe haemophilia A reporting median ABRs between 1.0 and 4.0 across Belgium, France, Germany, Italy, Spain, Sweden and the UK [3]. ABR in patients with moderate haemophilia was higher (2.0 to 8.0), suggesting patients with moderate haemophilia report an increased incidence of bleeding. However, moderate haemophilia has been previously associated with low annual joint bleed rates (AJBR), less haemarthropathy and burden of disease [5]. The findings suggested that European patients are undertreated, with treatment doses low across haemophilia types thus increasing the risk of bleed related complications and decline in joint health. In this study, 43% of bleeds occurred within soft tissue and joints, but the study failed to identify the prevalence of haemarthrosis in specific joints, therefore the specific implications of under treatment were not reported [3]. In addition, examination of United Kingdom Haemophilia Doctors Organisation (UKHCDO) National Haemophilia Database (NHD) bleed data has identified that patients with moderate haemophilia A with a bleeding phenotype, have ABR and AJBR similar to those with severe disease despite the suggestion they are less affected by bleeding and joint disease [4, 5]. Despite continuing, advancement in treatments across disease types and severity, such as extended half-life (EHL) products and reductions in CFC costs, reported ABR/ AJBR are still regarded as sub-optimal across Europe and the UK with low

tolerance for treatment dose (IU/kg) and regimes [3, 4]. Therefore the progression of joint diseases is likely to remain largely unchanged based on current pharmacological treatment.

Before the introduction of CFC prophylaxis, the knees were the most common site of haemarthrosis in children and adults with severe haemophilia [6, 7]. Since the introduction of prophylaxis, an investigation of bleeding patterns in children (n=55) and adults (n=45) by Stephensen *et al.* (2009) in severe haemophilia A identified that the ankle joint had become the most prevalent site of haemarthrosis and joint health deterioration [9]. Changing prevalence and patterns of haemarthrosis may emerge with the introduction of newer treatment products and increased interest in the effects of haemarthrosis on moderate haemophilia types. The current prevalence of ankle haemarthrosis is unknown, nor is its context understood in other at-risk joints of the upper and lower limbs.

Advances in the treatment of haemophilia with recombinant factor concentrate, EHL products, better inhibitor management and new anti-virial therapies means that the life expectancy of people with haemophilia has significantly increased [47]. Those individuals with moderate and severe haemophilia have a life expectancy that is 15 years and three years lower in severe and moderate haemophilia respectively, compared to the general population [48]. Although the gap between the general population and severe haemophilia is still significant, lower deaths rates caused by intracranial haemorrhage has seen the focus of treatment switch to the management of haemarthropathy and maintenance of joint health status [4, 49]. In those with severe and moderate haemophilia, it is paramount that haemarthropathy is reduced so that disability is minimised throughout their lives [50]. Despite some advancements, CFC treatment is still sub-optimal, and new therapies such as novel Factor bypassing agents and gene therapy are yet to evaluate their effect on the development of joint disease [3, 4, 51]. Therefore, haemarthropathy will remain a hallmark feature of the disease in people with

haemophilia who receive sub-optimal treatment or continue to present with clinical and radiological evidence of haemarthrosis and haemarthropathy [3, 4].

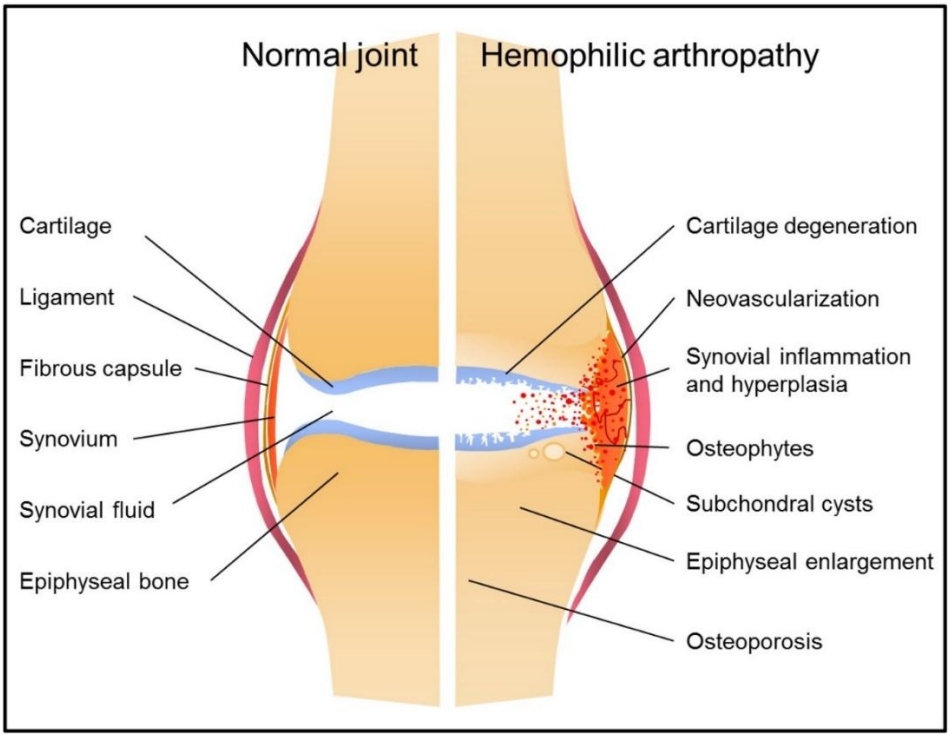


Figure 1: Schematic representation of a healthy joint (left) and haemophilic arthropathy (right) [52].

2.1.3 Haemarthropathy

Haemarthropathy is the most common clinical manifestation associated with severe haemophilia (Figure 1). Disability is a hallmark feature of the disease accounting for the majority of health-related complications [1]. Since the introduction of replacement CFC, the ankle has become the most common site of haemarthrosis, followed by the elbow and knee [9]. It is not fully understood why the incidence of haemarthrosis at the ankle has increased. A plausible cause is that during activities of daily living (ADL), the ankle is exposed to high compressive and shear forces, when combined with highly vascularised synovium and a shift in haemostatic balance, the risk of haemarthrosis is increased [9, 53]. Haemarthrosis causes blood products to accumulate within a joint, leading to inflammatory changes and eventual haemarthropathy [1]. When traumatic or acute joint haemorrhage occurs, patients often present with swelling, loss of function,

and pain [43]. Replacement CFC has seen a decrease in joint haemarthropathy. A pivotal study by Manco-johnson *et al.* (2007) compared the use of prophylaxis versus on-demand treatment in 65 haemophiliac children [33]. This randomised controlled trial (RCT) found that those children (n=32) treated with 25 IU/kg of factor VIII every other day (prophylaxis) reported a reduction in haemarthropathy. The prophylaxis group was then compared to a group that was only treated clinically on demand during a recognisable joint haemorrhage (40 IU/kg for 24 hours, 20 IU/kg at 24, 72 hours) over a mean period of 49 months. Patients randomised to the prophylaxis arm reported a dramatic reduction in haemarthrosis with an AJBR rate of 0.6 (SD 1.4) compared to 4.9 (SD 3.6) in the on-demand treatment group indicating the effectiveness of prophylaxis treatment. Despite the positive results of this study, changes reported by Magnetic Resonance Imaging (MRI) correlated poorly with clinical presentation. Similarly, the method of clinical assessment lacked the sensitivity to detect all clinically evident haemarthrosis [33]. Whilst the prophylaxis regime was effective at reducing bleeding, it does not protect against all haemarthrosis. This suggests that even those on primary prophylaxis, the gold standard of treatment, still experience episodes of bleeding that may not represent the patient-reported clinical signs and symptoms of haemarthrosis [54]. Undetectable subclinical and micro bleeding has been suggested as a potential mechanism for joint health decline but this is yet to be shown definitively [46, 55].

2.1.4 Pathogenesis of haemarthropathy

2.1.4.1 Pathophysiology

Haemarthropathy refers to secondary joint damage caused by a single significant or repeated minor incidences of haemarthrosis in people with haemophilia [56, 57]. In the presence of a single bleed, people with haemophilia report pain, swelling, warmth, loss of joint range of motion (ROM) and muscle spasm [58]. Haemophilic joint disease shares some characteristic joint changes with both rheumatoid arthritis (RA) and osteoarthritis

(OA), in the presentation of synovitis, bone reabsorption and articular cartilage degeneration [59, 60].

2.1.4.2 Synovitis

Synovial tissue lines the joints of the body providing lubrication, nutrition and facilitating the removal of waste products [57]. The synovial tissue is highly vascularised and where large or repeated haemarthrosis occurs, the synovium's ability to remove blood products is exceeded [61]. Haemosiderin is a by-product of haemoglobin, the oxygen-carrying protein in red blood cells, and has been identified as the main instigator of joint synovitis in people with haemophilia and the release of pro-inflammatory mediators [58]. In vitro studies have identified interleukin (IL) 1, IL 6 and tumour necrosis factor-alpha as the main cytokines that drive inflammatory response [59]. Repeated episodes of haemarthrosis and recurrent synovitis, results in abnormal vascularity that is particularly fragile and is more prone to bleeding, with associated synovial hypertrophy leading to a vicious circle of haemarthrosis and synovitis [52, 61].

2.1.4.3 Cartilage damage

Cartilage is an avascular structure made up of chondrocytes that maintains an extracellular matrix of cartilage, consisting of collagens, proteoglycans, and proteins. Cartilage when lubricated with synovial fluid facilitates smooth joint movement and resists compressive and shear forces during joint loading [57]. As a result of haemarthrosis and in conjunction with fibrosis of the synovial lining, the joint cartilage becomes damaged [58]. Changes to hyaline cartilage are both chemical and mechanical in aetiology. Iron-catalysed reactive oxygen intermediates induce apoptosis of the chondrocytes leading to changes in the composition of the articular cartilage matrix [61]. Contamination of the joint with 10% and 20% blood products over a 48 hour period, has been shown to change cartilage matrix properties causing irreversible damage [57, 62]. Eight-week exposure resulted in more deformable cartilage, with less resistance to shear forces when compared to a control group which may provide insight into the changes in vitro [58]. Recent advances in MRI have challenged the concept that cartilage damage

occurs by pro-inflammatory mediators released from haemosiderin-burdened synovium alone. MRI of cartilage from weight-bearing symptomatic joints (knees and ankles n=16) with concurrent histological analysis using post-operative joint arthroplasty tissue identified direct iron deposition within cartilage chondrocytes [63]. Iron accumulation within the cartilage plays a direct and continuous role in cartilage toxicity, independent of synovial changes. The potential for this MR “iron” imaging technique is timely, with bleed rates reducing and a paradigm shift in treatment. The potential to use this sequence and identify iron deposition within cartilage as a biomarker for subclinical joint changes are promising but sequencing is yet to be refined or validated in people with haemophilia.

2.1.4.4 Bone damage

The mechanism by which bone damage occurs is yet to be established in haemarthropathy [59]. The process of degenerative bone damage is thought to be similar to that of OA with the chronic inflammatory process seen in RA [58, 59]. Bone changes occur in the presence of cartilage damage, but not in isolation. The initiation of osteoclastogenesis, which is enhanced by cytokines, is thought to initiate inflammation and bone reabsorption caused by an imbalance of bone turnover by osteoclast and osteoblasts. Osteochondral changes in haemarthropathy include erosion, cyst formation, osteonecrosis and eventual joint failure [64]. The risk of bone damage is complicated by an increased incidence of osteoporosis, which occurs in the presence of infectious comorbidities such as hepatitis C, and human immune-deficiency virus (HIV) [65]. Loss of bone mineral density (BMD) has been reported in this population and may contribute to the advancement of haemarthropathy [66]. In haemophilic children, the presence of low BMD has been associated with the reduction of activity and parental fear of bleeding, resulting in periods of inactivity related to joint bleeds [67]. In the pathogenesis of haemophilia, reduced BMD may further complicate the multifactorial nature of haemarthropathy and damage. In established haemarthropathy, plain film radiographs

identify osteonecrosis, epiphyseal overgrowth, bone cyst formation, and bone fusion [68, 69].

In advancing ankle haemarthropathy, subchondral cyst formation is often featured on diagnostic imaging. The presence of bone cysts with the tibia and talus represent not only advancing disease but changes to the joint contact pressures. Finite element (FE) modelling has shown cyst formation in the tibia increases joint contact pressure by a mean of 77% (SD 48%) and in the talus increases by 66% (SD 107%) [70]. The cartilage contact pressures also increased by 120% (SD 145%) indicating increases in contact pressure are not exclusive to the bone. The presence of increased contact pressure values may affect joint health with the potential to increase the rate of joint disease. This is the first study to model the changes of ankle haemarthropathy and contact forces and whilst published as an abstract, it shows promise in understanding the effects of bone cysts on joint health [70]. The combination of synovitis, cartilage damage and bone pathology leads to fibrosis of the joint and ultimately destruction [53]. In weight-bearing joints such as the ankle, the process of deterioration leads to potential functional changes in gait and structural changes and subsequent decline in patient-reported pain and disability [18].

2.1.5 The haemophilic ankle

The ankle joint complex (Figure 2) consists of multiple articulations that facilitate functional movement of the body over the foot. The ankle and foot are made up of 28 bones including the tibia and fibula form a total of 33 joints. Specifically, the ankle joint complex is made up of several articulations of the talocrural joint (tibiotalar), subtalar joint talocalcaneal and talonavicular joints [71, 72]. OA of the talocrural joint referred to as the “ankle joint”, secondary to haemarthrosis, is common in moderate and severe haemophilia. It has been hypothesised that increased physical activity in combination with the mechanical demands required of the ankle joint during ADL, expose the ankle joint to greater compressive and shear forces [73]. Pathology of the foot and ankle is predominantly reported at the ankle joint, with the subtalar joint affected in >50% of cases

[74]. The articulations of the talonavicular and calcaneocuboid joints are rarely affected by haemarthrosis, however secondary OA related to the biomechanical failure of the proximal subtalar and ankle joints are reported [75, 76].

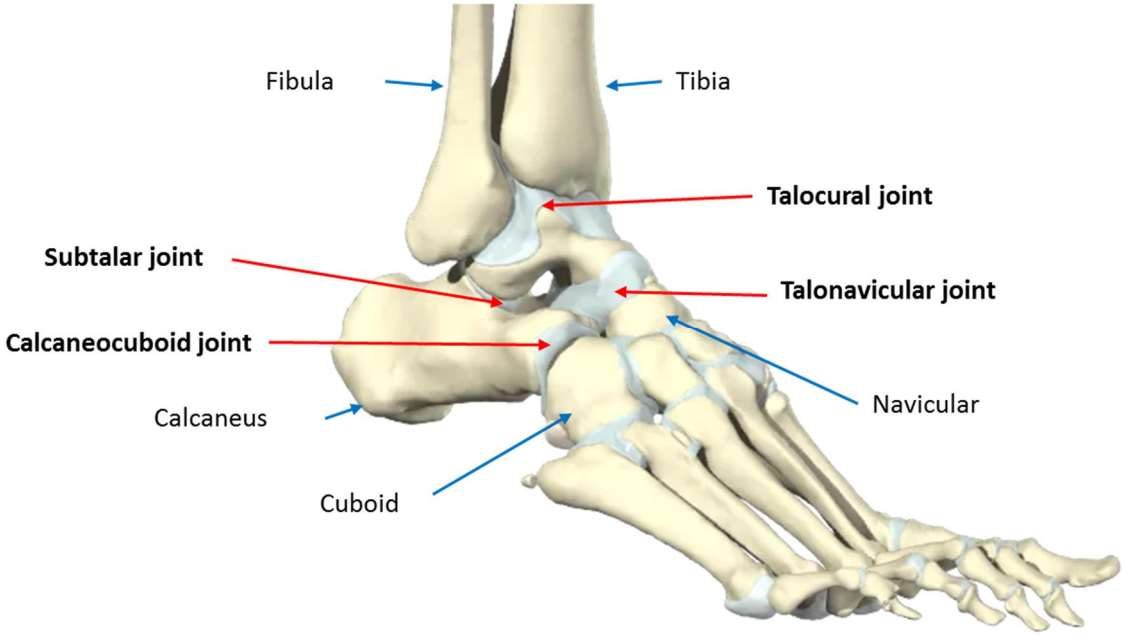
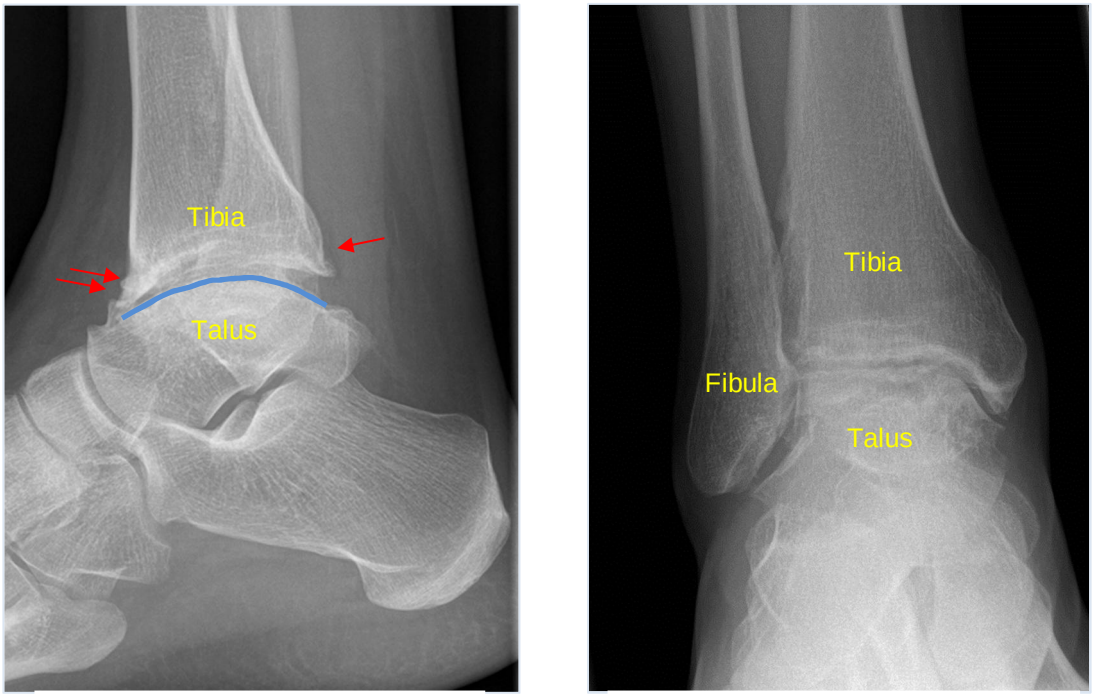


Figure 2: Anatomy of the ankle joint complex

(Primal pictures 2021, image produced for thesis)

Although an inherited condition, people with haemophilia experience incidents of bleeding in the early years of life. Repeated episodes of haemarthrosis lead to the formation of abnormal highly vascularised synovium with excessive blood flow to the epiphyseal plates [77]. Increased blood flow to growth plates leads to accelerated ossification and growth of the epiphyses resulting in angular deviations such as tibial rotation at the ankle joint and potential for leg length discrepancies [78]. Structural joint changes appear to occur during the second decade of life with the formation of osteophytes, driven by chronic synovitis [68, 79]. At the ankle joint, osteophyte formation is seen at the anterior margin of the tibia but can occur posteriorly in end-stage joint disease [80]. The occurrence of osteophytes (Figure 3) further complicates the risk of haemarthrosis by synovial impingement during dorsiflexion and plantarflexion [64]. Osseous hindfoot eversion with significant foot deformity is associated with disease of

the subtalar joint, a common site of disease activity seen in inflammatory arthritis [77, 81, 82].



4a: lateral view **4b: Anterior/ posterior view**

Figure 3: Radiographs of the ankle joint with haemarthropathy in a 26-year-old male

Figure 3a: Changes to joint geometry of ankle joint and loss of joint space. The blue line represents the shape change of the talar dome and red arrows identify sites of osteophyte formation. **Figure 3b:** Loss of joint space at the ankle joint and irregularity of the joint surfaces (fibula, tibia and talus)**.**

Progression of haemarthropathy of the ankle joint leads to plantarflexion deformity due to further osseous and soft tissue changes at the ankle joint. Where bleeding occurs in the gastrocnemius and soleus muscles of the lower limb, soft tissue contracture and scar tissue formation occur leading to plantarflexion. This further changes the anatomical structure of the ankle joint as well as leading to functional changes [80]. Talar dome necrosis has been reported in children with haemophilia but only in a small number of case reviews (n=4), with changes in geometry and subchondral bone cyst formation [83, 84]. A study of people with haemophilia undergoing radioactive synovectomy (n=9, 19 joints) reports 50% of study participants having subtalar joint involvement, but all

participants had an inhibitor, requiring a bypassing clotting factor concentrate, which does not represent typical treatment and therefore may have affected results [85]. A recent publication by Lobet *et al.* (2017) highlighted the significant contribution that subtalar joint disease may play in the progression of foot deformity as the ankle joint becomes limited in function [86, 87]. This is contrary to earlier research that reported that whilst the subtalar joint is affected in isolation to the ankle joint, 50% of affected patients in a study of ankle haemarthropathy had some form of subtalar joint disease [85]. The pathological changes reported in ankle haemarthropathy lead to changes in ankle joint structure and impact on function [19].

The biomechanical changes related to haemarthrosis and haemarthropathy are discussed in section 2.2.1.2. Firstly the biomechanics of the ankle, data collection methods and modelling are presented to provide context to changes reported in haemophilia.

2.2 Ankle joint biomechanics

Biomechanics of the ankle joint in normal and pathological haemarthropathy are presented in section 2.2. The current methods of modelling the kinetics and kinematics of the lower limbs and foot and ankle are also described.

The ankle joint forms a kinetic linkage between the lower limb and foot allowing interaction with the ground, providing a platform for gait. The ankle joint forms the connection between the tibia, fibula and the talus with the load-bearing surface of the joint occurring at the tibia and talus interface [72]. Movement at the ankle joint occurs mainly in the sagittal plane in plantarflexion and dorsiflexion (Figure 4) with up to 20° of dorsiflexion and 45° of plantarflexion ROM, although during ADL such as walking, the ankle joint only requires 30° ROM [88]. The subtalar joint is formed by the articulation of the talus and calcaneus and forms a tri-planar, uniaxial joint with the tibia. The geometry of the subtalar joint permits inversion and eversion of the foot allowing adaption to uneven terrain during ADL [89]. The foot is in a slightly supinated position at heel strike

(heel rocker) and pronates through the midstance phase of gait (ankle rocker) before the foot begins to supinate in preparation for propulsion (forefoot rocker) [90].

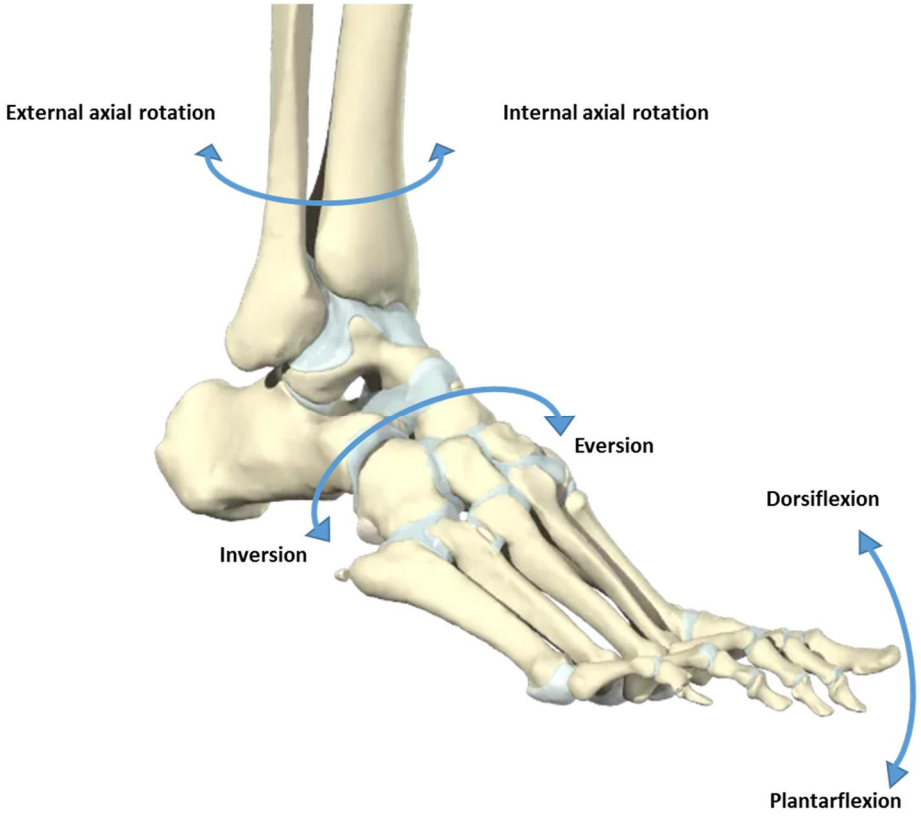


Figure 4: Foot and ankle motion in the sagittal, frontal and transverse planes

(Primal pictures 2021, image produced for thesis)

Ankle joint geometry means that when fully dorsiflexed, the ankle is at its most stable (closed packed position). Forces are transferred across the talar dome and account for 77-90% of load with the remaining force (10-23%) transferred across the medial and lateral talar facets [71]. The over simplification of the ankle as a simple hinge joint has been challenged by Leardini *et al.*(2018) who identify the ankle as a complex biomechanical structure playing a fundamental role in gait and ADL [88]. Specifically, the complex interaction between the talocrural and subtalar joint provides the three ankle rockers for normal motion during the walking cycle [88]. The first rocker is described as the heel rocker, the second the ankle rocker and the third, the forefoot rocker (Figure 5).

The heel rocker (Figure 5a) describes the point at which the heel makes contact with the floor (heel strike). Gradual plantarflexion occurs until the forefoot makes contact with the floor. As the ankle rocker (Figure 5b) starts, the shank progresses over the ankle joint causing gradual dorsiflexion of the ankle until the point at which the heel starts to lift. During this third rocker (Figure 5c), the foot is maximally dorsiflexed and the heel lifts off the floor. The foot generates power through plantarflexion and continues until maximum plantarflexion is achieved and “toe-off” occurs leading to the swing phase of gait [88].

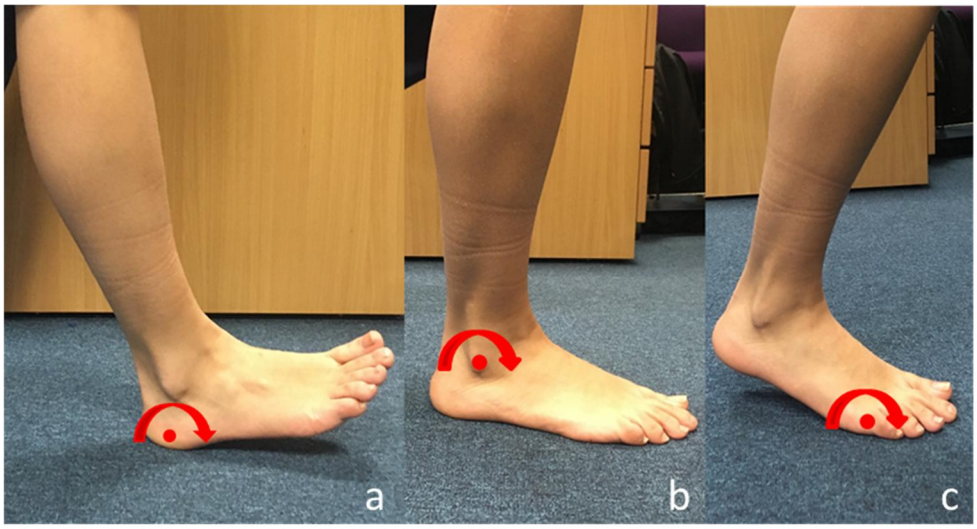


Figure 5: Ankle rockers

a first rocker, **b**: second rocker **c**; third rocker (Image produced for this thesis)

In non-pathological gait, at heel strike during the first ankle rocker, GRF is posterior to the ankle joint centre creating a small external dorsiflexion moment as the dorsiflexors (anterior muscle group) contract to control the rotation of the foot onto the ground, preventing foot slap (Figure 6). From heel strike, GRF passes anterior to the ankle (second rocker) creating an internal plantarflexion moment that increases with the posterior muscle group concentrically contracting towards toe-off (third rocker) [89, 91].

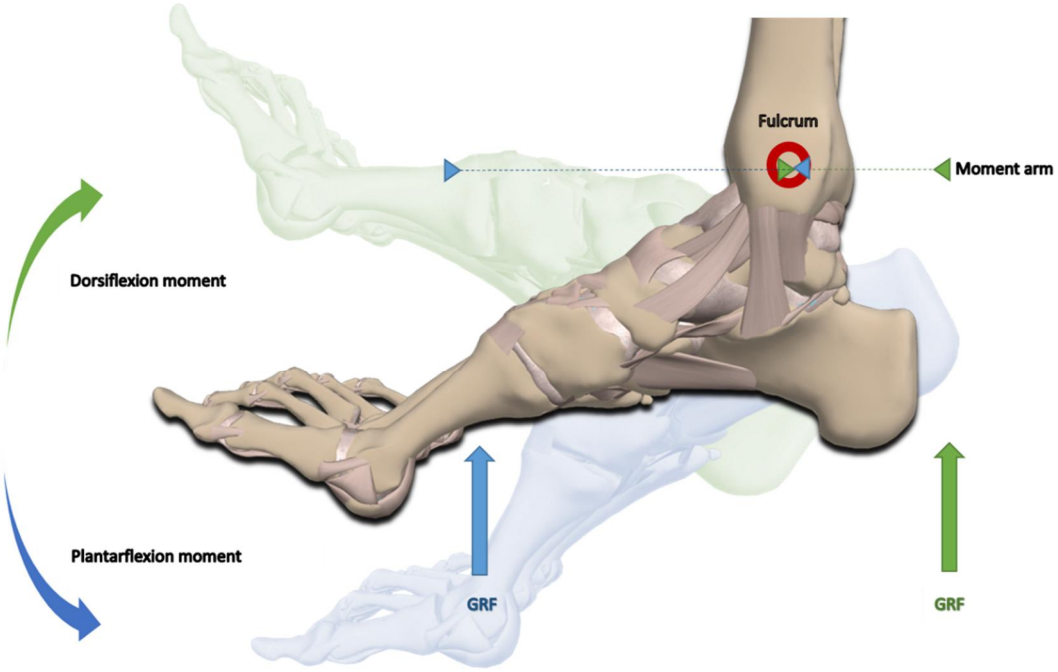


Figure 6: Ankle moments

Sagittal plane external dorsiflexion moment and internal plantarflexion moment (Primal pictures 2021, image produced for thesis)

2.2.1 Kinematics and kinetics of the lower limb

Observation of the human body during walking or evaluation of the kinetics and kinematics of the lower limb seeks to understand the effect of pain and disability on biomechanical function [89]. Instrumented mats may be used to obtain temporal and spatial parameters of gait, which record outputs such as walking speed and stance time, providing measures of walking function [92]. The measurement of joint angles and positions (kinematics) and the observation of forces acting on joints (kinetics) require a more sophisticated method of measurement [91].

2.2.1.1.1 Lower limb models

Quantification of the kinetics and kinematics in normal and pathological locomotion is undertaken using 3D gait analysis, often using an infrared camera system that tracks passive reflective markers [91]. Skin mounted markers are placed on the segment or

body segments of interest as the individual moves/walk through the capture volume with the 3D trajectory of each marker captured (Figure 7) [93]. 3D motion capture systems and force plates allow for the calculation of 3D temporal/spatial, kinematics and kinetics. Data acquisition requires the placement of reflective markers on specific anatomical landmarks and segments to provide 3D spatial positions, such as the axis of the knee where alignment requires accurate placement to capture the knee varus/valgus and flexion-extension ROM [91].

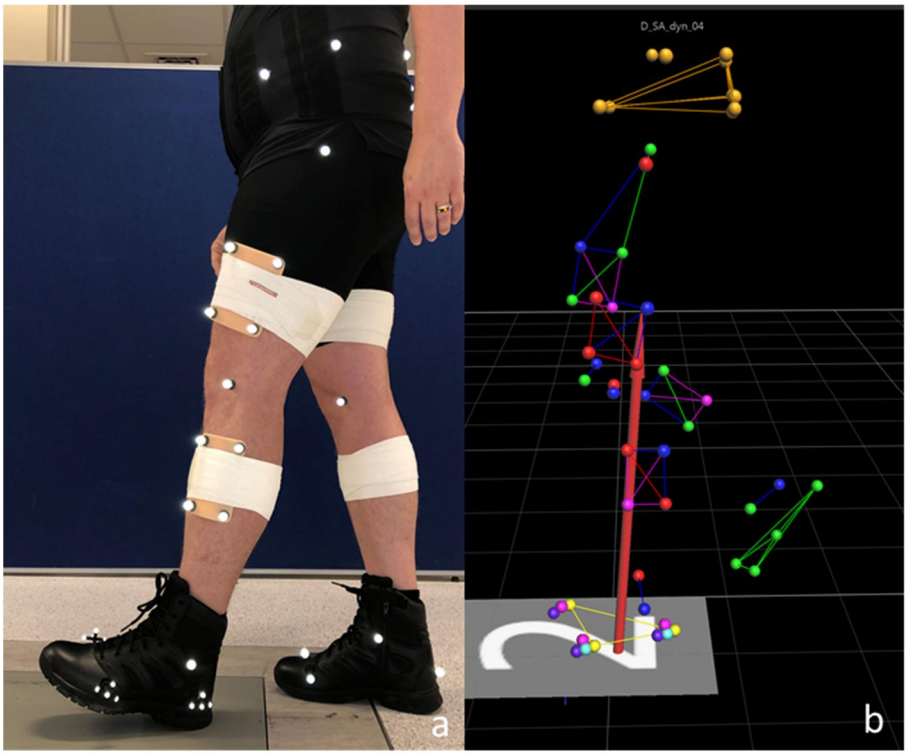


Figure 7: Segment tracking
a: gait laboratory, b: Vicon 3D gait system visualisation (C-Motion, Germantown, USA)

There are two common biomechanical gait models, the “conventional gait model” and the “Calibrated Anatomical System Technique” (CAST) [91]. The conventional gait model, such as Plug-in-Gait (PiG, Vicon Motion Systems, Oxford, UK) uses computational methods that assume the markers are rigid and attached to bony landmarks and segments [94, 95]. Joint angles are then calculated using Cardan angles between adjacent segments defined by the 3D position of the markers.

PiG is commonly used and widely adopted in clinical gait analysis laboratories [95]. The PiG model requires fewer marker trajectories (16 markers) when compared to more sophisticated models, and benefits from a reduction in data collection times and therefore is more conducive to clinical research and practice [96]. The PiG has been more widely validated than any other model and its repeatability has been established in multiple studies [97-100]. However, the accuracy of the PiG model has been challenged. Predictive methods used to calculate joint centres are known to incorporate error due to marker misallocation, skin movement artefact and inaccuracies of subject measurements such as ankle width used to calculate joint centres [101-103].

In an improved approach, an inverse dynamics model is used to calculate kinetics around the kinematics. The joints are linked by segment kinematics, external force data and input of anthropometric and inertial characteristics derived from cadaveric studies [104, 105]. The CAST was developed by Cappozzo *et al.* (1996) to standardise movement description in research and clinical practice and is classed as the gold standard protocol for 3D kinematic analysis [91, 106]. The CAST model is different to the PiG as it uses tracking pads to track segments, rather than a single marker, therefore reducing skin, anatomical frame and location artefact [107]. The use of the CAST model has shown less tendency to incorporate errors when generating ankle kinetics. The addition of the medial malleolus marker within the anatomical reference frame (medial and lateral malleolus) provides a better estimation of the ankle joint centre. [108].

The variability of different gait models assessed by Ferrari *et al.* (2008) [109] was undertaken using a single marker set made up of 60 markers in three asymptomatic subjects. Both the CAST and PiG models were compared with other lower limb biomechancal models (Total 3D Gait (T3Dg), Servizio di Analisi della Funzione Locomotoria (SAFLo) and Laboratorio per l'Analisi del Movimento nel Bambino (LAMB)). General uniformity was found between the PiG and CAST models with good consistency for sagittal plane joint angles and kinetic variables especially at the ankle ($r>0.988$, $p<0.001$). The frontal plane mean error was small in the CAST model mean error of up

to 2.5° (2.2SD) (LAMB, SAFLo, T3Dg) when compared to PiG (8.1°, SD 8.2). Therefore findings suggest the CAST model is more robust in all three planes when modelling the lower limbs.

2.2.1.1.2 Modelling of ankle kinetics and kinematics

The complexities of the foot and ankle are subject to theoretical concepts and paradigms of foot function and its relationship to ankle biomechanics in normal and pathological gait [110]. The association of segments at a single joint such as the knee are relatively straightforward in marker placement and segmental kinematics, but the large number of bones and articulations in the foot makes biomechanical modelling complex [111].

Any single segment foot model treats the foot as a single segment linked to the shank to generate ankle kinetic and kinematic data [106]. This method is relatively simple and when the complexities of the foot can be ignored, a majority of biomechanical studies use this approach. This can be due to the aim of the study where the complex interaction of the foot is not required and for simplicity in data collection methods [91, 99]. Single-segment foot models report kinematic changes at the ankle in the presence of ankle pathology [19, 112-114]. Limitations of ankle and foot modelling are reflected in the criticisms of PiG and its reliance on anatomical and tracking markers to calculate ankle joint forces, associated with incorporation of error, single-axis 2d modelling and the requirement of additional markers to obtain inversion/ eversion foot data [100]. A single segment approach is acceptable when assessing the pathology of the ankle. The axis of the ankle joint is primarily in the sagittal plane, therefore a single segment foot model would provide the necessary detail to report kinematic changes associated with pathology such as ankle haemarthropathy. Movement at the ankle joint occurs mainly in the sagittal (65-75° ROM) and transverse planes (35° inversion/eversion) [72]. A single segment foot model with six degrees of freedom would therefore capture the necessary data to quantify changes in ankle kinetics and kinematics.

3D multi-segment foot modelling has become increasingly used in research and clinical practice where the foot is divided into smaller functional segments, allowing the quantification of movement between coupled units such as the hindfoot and forefoot. This is of particular importance in the foot where pathology may be isolated to single joints within the foot, such as the first metatarsal-phalangeal (MTP) joint where OA changes are common [115]. Skin mounted markers are the most common method of obtaining kinematic data and be adequately reliable when compared to the "gold standard" intra-cortical pins [99, 111, 116]. Two of the most widely cited in multiple clinical research studies multi-segment foot models are the Oxford Foot Model (OFM) and Leardini foot model [20, 99, 111]. The OFM divides the foot into four segments (tibia, hindfoot, forefoot and hallux) and the Leardini foot model uses five segments (shank, calcaneus, midfoot, 1st metatarsal and proximal hallux) [117, 118]. In particular, the OFM is used for gait analysis in adults and children and demonstrates strong reliability, but to date validation of both models has been limited by a small sample size limiting inference to large populations [99]. Another limitation of a multi-segment foot model is the calculation of ankle kinetics, which are limited to single segment calculation [99]. The multi-segment models that incorporate kinetics are too complex for use in clinical practice and limited to a small number of experimental studies [119, 120]. This is due to the complexities of calculating the inertial properties of the foot with multiple articulations, muscles, tendons and variations in alignment. Similarly, there is no one universally adopted multi-segment foot model where the inertial properties could be established, limiting standardised adoption of a multi-segment kinetic foot model [99]. Attempts have been made to calculate multi-segment joint kinetics using segmental inverse dynamic models to divide the foot up based on the combination of segment coordinates and compared to a single segment PiG model [121, 122]. In both studies, the single segment foot model over reported ankle sagittal plane ROM of between 2.5 and 3.6 degrees, but peak plantarflexion moments were not affected in either study [121, 122]. Both studies were limited by small samples (n=10) therefore lacking the power to make any definitive

conclusions. The methods used to calculate ankle joint kinetics and kinematics may therefore be overly complicated in clinical research and a single segment approach remains the most appropriate method to calculate ankle joint kinetics [121, 122].

2.2.1.1.3 In-shoe foot kinematics

The quantification of foot movement within footwear provides a further level of complexity when modelling foot and ankle kinematics [123]. The use of shoe-mounted markers make assumptions that foot and ankle kinematics are representative of foot movement within the shoe, but there is an emerging body of evidence that suggests this is not the case [123]. During activities such as walking and running, the foot moves within the shoe presenting the possibility of larger inaccuracies of measurement in “true” foot position relative to the 3D space incorporating error by under/over-reporting of kinematics.

Differences between the tibio-calcaneal kinematics of skin and shoe-mounted markers have been investigated by Sinclair *et al.* (2013). Kinematics were measured using a 3D analysis system with widows cut within an athletic running trainer [124]. Findings indicate that shoe-mounted marker sets under-report foot kinematics during gait and therefore have the potential to misinterpret foot and ankle kinematics.

Similarly, Alcantara *et al.* (2018) compared skin mounted calcaneus and footwear mounted markers [125]. Significant differences ($p =< 0.001$) were reported in ROM with shoe-mounted markers under-reporting ROM at the calcaneus by 5.9° sagittal, 1.5° frontal and 1.5° in the transverse planes. Three 25mm holes were cut into the heel, which has since been recommended as optimal hole size when collecting in-shoe data supporting data collection methods. However, the proximity of holes raises questions about shoe integrity which may increase movement within the shoe and therefore over report kinematic data [126]. Observation of midfoot OA and subsequent pain have been compared in barefoot and in gait shoe conditions [127]. A plimsoll with a 6mm thick rubber sole unit and fabric upper contained windows to allow placement of a foot-mounted OFM marker set. Hindfoot sagittal and frontal plane motion obtaining coefficient

of multiple correlations (CMC) of 0.967 and 0.981, respectively. Halstead *et al.* (2016) work contradict the findings of the previously mentioned studies in that both hindfoot conditions were similar [127]. The shod footwear condition examined in a research setting shows promise for the evaluation of in-shoe orthotic devices, but does not represent the more structured footwear type used in clinical practice. Whilst limitations are acknowledged by the author windows cut into the shod upper may have affected structural shod integrity, therefore, incorporating measurement error. Also, the use of a single kinematic trial for analysis is not the convention in gait analysis [111]. Higher numbers of trials are reported to increase the reliability of gait parameters. Comparison of a single trial to five representative trials reports lower values of repeatability and larger variability in between subject values in single-trial studies [111, 128].

There are several limitations to the use of in-shoe foot modelling. Firstly, the size of the window in which the marker is placed, secondly the type of markers used and thirdly changes in the structural integrity of footwear when incorporating windows. Several studies have used windows of varying sizes to analyse optimal size [125, 127, 129]. The size of the hole within the shoe may introduce contact artefact with the marker fouled by the margin of the shoe if too small, introducing error to the gait model. Bishop *et al*. (2015) investigated shoe hole size effect on movement and segment motion of marker hole fouling and contact artefact [126]. Three different footwear conditions were altered with circular holes of different sizes (15, 20 and 25mm), with marker trajectories mounted on wands placed through windows at the medial, lateral and posterior calcaneus and the 1st and 5th MTP joints. Only marker placement in the 25mm condition did not exceed the radius at all sites. Likewise, the 25mm condition was most similar to the barefoot condition, with similar isotropy index scores, a measure of the marker movement within the hole (no significant scores between conditions). Bishops *et al.* (2015) study used a 25mm wand that protruded from the hole with the marker mounted at the distal end. The wand facilitated better clearance from the 25mm hole and they recommend that the wand diameter should not exceed 4mm in width (compared to a standard 9mm marker) [126].

Cutting larger holes in footwear appears to compromise structural integrity. Loss of heel contour stability of 10% has been reported by Butler *et al.* (2006) when cutting a single hole in a shoe heel contour [126, 130]. It seems obvious that hole size and the amount of material removed should be minimal for the chosen foot model. Removal of large portions of the footwear upper that compromise shoe integrity may not be suitable for more robust footwear such as a military boot [127, 131].

2.2.1.2 Biomechanics of ankle haemarthrosis and associated haemarthropathy

Early observations of the biomechanical effects of haemophilia on the immature ankle reported changes to the articulation position with gradual plantarflexion with hindfoot valgus/varus and loss of ROM [8]. Changes in foot position as a compensatory mechanism, caused by knee flexion deformity have been attributed to adaptive limb length differences [77]. Biomechanical changes to the lower limb are further confounded by muscle atrophy, neurological deficit, axial deformity and structural changes [86].

In children and adolescents, the biomechanical changes associated with haemarthrosis and haemarthropathy are reported in only a small number of studies. Young children aged 7-13 on prophylaxis treatment (n=14) with a target ankle joint, report similar temporal and spatial and sagittal plane ROM to age-matched controls. However greater mean knee ROM was reported in the haemophilia group of (22.2 SD 8.77°) compared to normal (16.0 SD 6.08°; $P< 0.05$) with significant increases in knee flexion moments (0.35 Nm/kg; $P < 0.05$), ankle plantarflexion moment (0.10 Nm/kg; $P < 0.05$) and hip flexor moment (−0.31 Nm/kg; $P< 0.05$) in the haemophilia group. It is unclear if the patients' target joint was measured in isolation or both limbs were used to collect kinetic and kinematic data. This may have affected results with potential findings lost in the inclusion of the unaffected limb. The biomechanical methods used are known to incorporate error by how joint centres are defined, therefore moment data may not be reliable in this small sample [101-103]. The treatment regime was not reported which may have affected patients. A "target joint" would suggest that the cohort of participants

were not adherent to treatment, or were undertreated therefore limiting the generalisability of findings. However, changes in moments suggest whilst the clinical signs of ankle joint pathology are low (≤2 of 25) there are measurable mechanical joint changes [73, 132].

In older haemophilia children aged 11-18 years, significant differences in stance time 59.0% (1.3 SD) and 57.8% (1.4 SD, P<.03) and swing time 41.1% (1.3 SD) and 42.3% (± 1.37SD, P<.03), are reported between control and haemophilia groups respectively however the difference are small in magnitude despite significance [133]. No differences were reported in sagittal plane kinematics at the ankles, knees and hips. Self-reported bleed rates were collected, but with no clinical measure of joint health, it is unclear how finds apply to biomechanical parameters in the absence of pathology. Data produced by Suckling *et al.* (2015) and Stephensen *et al.* (2009) indicate whilst gait changes occur in children and adolescents with haemophilic ankle haemarthrosis, they predominantly affect ankle joint moments [73, 134].

In adults with established ankle haemarthropathy, biomechanical changes are more apparent. Changes in both ankle joint structure and function do not present until later years [132]. In one gait reproducibility study undertaken by Lobet *et al.* (2010), changes were identified in adults (n=18) with severe and moderate haemophilia during the push-off phase of gait ankle. Power generation decreased, with compensatory increases at the hip and power absorption at the knee during swing. One incidental finding of the study identified that over the 18 week period biomechanical parameters declined [135]. Calculation of mechanical lower limb workings (kinetic movement of segments in relation to the bodies centre of mass) reported recovery index score a measure of the efficacy of gait mechanisms to passively recovery energy whilst walking, decline from 65.4% (SD 8.0) at baseline to 63.3% (SD 7.9) at follow-up (P=0.01) representing a 3.2% impairment between visits [135]. The author suggests this decline represents the natural progression of joint damage. Whilst the findings of this study provide insight into decline over time

several factors may have influenced findings, such as pain levels, bleed incidence and patients QoL.

Radiological, clinical and 3D gait parameters have been compared in adults with haemophilia and ankle haemarthropathy. Foot function index-revised (FFI-R) subscales of pain and stiffness were compared to ankle power, an objective 3D gait parameter that can be used to represent ankle function [19]. No significant differences were reported between clinical and radiological scores and ankle function and therefore clinical and radiological scores alone did not predict joint function. In clinical practice, patients with radiological evidence of ankle haemarthropathy continue to function reasonably well for many years and therefore reliance on clinical and radiological measures alone may not provide a true measure of function [77]. Lobet *et al.* (2010) concluded that radiological and clinical scores do not properly integrate joint function, supporting the use of 3D gait analysis as a measure of function in adults and children with haemophilia [135].

In the presence of multiple joint haemarthropathy, Lobet *et al.* (2012) using 3D lower limb kinematics reported no changes at the knee, but a significant reduction in ankle ROM ($P<0.001$) and hip ROM ($P<0.001$). Centre of mass variation in vertical displacement was also significantly higher ($P<0.001$) resulting in lower muscle efficiency and increased net energy consumption. Mechanical changes associated with multiple joint involvement appear to lead to greater energy consumption, but in this study, cohort participants adopted a walking strategy to compensate. In a similar follow-up study the impact of ankle haemarthropathy was studied and its effect on energetic and mechanics of gait [18]. When compared to healthy controls changes in kinetics and kinematics of the ankle resulted in increased stance 64.1% vs 61.4% ($P=0.012$) in the ankle and control group respectively. Kinematics at the ankle indicated significant mean changes at the ankle during the push-off (third rocker) (−2.55° (0.82) $P<0.001$) with the ankle OA group achieving a mean value of 16° of dorsiflexion compared to the control group of 28.7°. Ankle peak plantarflexion moment (Nm/kg^{-1}) was also higher (1.19, $P=0.031$) than the control group (1.06). One explanation provided was the presence of bony deformity

limiting ROM. Additional work may be required from the proximal joints by means of compensation, with lower knee peak flexion moments (P=0.001) positive hip flexor power during early swing (P=0.001) and lower peak knee extensor moment (P=0.004) during loading and lower peak eccentric knee extensor power during swing.

More recently, the association of MRI features of ankle haemarthropathy and clinical gait features have been explored using multi-segment foot modelling. Eerdekens et al. (2020) conducted an observational study of 48 ankles with ankle haemarthropathy [136]. A large negative association was found between ankle joint peak power and MRI scores (ρ = −0.631; p = <.001), based on increasing osteochondral sub-scores (P= −0.701; P= <.001), the worsening severity of synovial hypertrophy (P= −0.507; P = <.001) and progressive haemosiderin deposition (P= −0.400; P=0.005). Association was found between osteochondral IPSG-MRI scores and ankle joint peak power absorption. The results indicated that in the presence of ankle haemarthropathy, there is a reduction in ankle joint mechanical loading during walking. Whist the sample size used in this study was small (n=48 ankles/ 24 participants) the data provides insight into the mechanical effect of severely damaged ankle joints. Specifically, in the presence of severe ankle haemarthropathy, there is a decrease in absorption of power, potentially caused by pain, muscle atrophy and/or weakness.

In people with haemophilia, kinematic analyses of sagittal plane motion have reported a strong correlation with patient-reported ankle pain and changes in movement [18]. Haemarthropathic structural changes at the ankle joint are associated with a reduction in peak power generation, reduced stride length and greater energy expenditure due to compensatory gait changes at the hip and knee [18]. Function is further impacted by the loss of muscle mass, muscular damage due to repeated bleeding and reduced activity [137]. Loss of muscle mass and proprioception consequently proceed functional impairment at the ankle. Finally, the proprioceptive changes lead to an inability to maintain dynamic joint stabilisation and the functional inability to protect the ankle joint

complex from ground reaction forces and shear further exposing the ankle to greater biomechanical stress [53, 86, 137-139].

2.3 Management and treatment of ankle haemarthrosis and haemarthropathy

The literature presented in section 2.3 provides an overview of the methods currently adopted in the management of ankle haemarthrosis and the resultant haemarthropathy. This section, therefore, contains an overview of physical, injectable and surgical management of the ankle. Details of current research of foot orthoses and footwear management of ankle pathology in haemophilia are also presented.

2.3.1 Physical rehabilitation

Maintenance of good musculoskeletal (MSK) health is paramount in the avoidance of soft tissue bleeding and haemarthrosis. Multiple studies have now suggested physical activity should be undertaken to maintain function, structure and good bone health [140]. Exercise as a prescription has been widely researched in haemophilia [141]. The ageing population and the increased life expectancy of those patients on regular treatment now increase the need for the management of multi-morbidities. The use of physical therapy is well established in the management of ankle haemarthropathy and forms part of the World Federation of Haemophilia (WFH) and UKHCDO recommendations for the management of acute and chronic joint bleeds [25, 43]. Rehabilitation aims to reduce pain, restore normal functional values of body strength, muscle tone, ROM and prevent disability [142, 143]. Following acute episodes of soft tissue bleeding or haemarthrosis, a period of immobilisation is recommended until the pain subsides. Rehabilitation is then focused on the restoration of joint strength and mobility. In the acute stages of haemarthrosis ‘protection, rest, ice, compression and elevation’ (PRICE) therapy forms part of the UKHCDO guidelines [43]. Management in the initial stages of haemarthrosis requires joint rest and protection to relieve acute pain and reduce the risk of repeated

bleeding and prolonged exposure to blood products. Therefore a period of non-weight-bearing at the ankle may reduce the risk of joint damage by reducing mechanical stress to the ankle joint [144]. Diagnostic MSK ultrasound evaluation of joints following haemarthrosis has identified that despite the subsidence of pain, the joint may still contain blood products that exacerbate synovitis and change cartilage properties [145]. Deficiencies in proprioception have been identified following haemarthrosis resulting in reduced joint stability which further supports the requirement for immobilisation. Prolonged immobilisation may also have an impact on overall strength, ROM and dynamic joint control, therefore immobilisation should be kept to a minimum or where clinical symptoms of pain in combination with the restoration of ROM are evident [146]. No consensus has been produced on what is regarded as the optimum duration of immobilisation. This is due to the variable nature and severity of presentation, although the WFH recommend non-weight-bearing until the pain subsides, with empirical evidence from Rodriguez-Merchan *et al.* (2008) suggesting non-weight-bearing for four days [147]. In reality, the clinical presentation dictates the length of time non-weight-bearing is required. In the presence of synovitis and ankle haemarthropathy, maintenance of trough levels to halt bleeding is paramount. Where joint damage has occurred, physical therapy recommendations from the UKHCDO are based on identifying mechanical causes associated with arthropathy and referral for conservative interventions such as radioactive synovectomy. Physical therapy maintains joint ROM, prevents mechanical changes that increase the risk of haemarthrosis and haemarthropathy and decreases patient-reported pain and disability and improves QoL.

2.3.2 Intra-articular therapy

Intra-articular (IA) therapy has been investigated more than any other approach in the non-surgical management of foot and ankle OA [148]. A recent systematic review of IA therapy in foot and ankle OA and RA reported 22 studies, but only five RCTs of IA

injection therapy in foot and ankle OA. In haemophilia, IA therapies such as corticosteroid, viscosupplementation and platelet-rich plasma (PRP) have the potential to aid rehabilitation and reduce the burden of joint disease.

2.3.2.1 Corticosteroid

The use of IA corticosteroid is beneficial in the modification of disease activity and suppression of joint inflammation in OA as an adjunct therapy [149]. In haemarthropathy, evidence for use is limited to small studies and narrative reviews; orthopaedic management of disease and clinical opinion on the effect demonstrate anecdotal benefits between two and four weeks after injection [23, 150]. In a small study (n=10) of patients who did not respond to CFC, IA injection of 80mg of methylprednisolone was used to treat haemarthrosis induced knee synovitis. The patients were followed up over 12 months and demonstrated reductions in synovitis. Scoring methods used to describe improvements and patient treatment regimens were not reported. Therefore over the 12 month period it is unclear if the IA corticosteroid reduced synovitis, or a change in CFC treatment with higher troughs and different products were used, which would have a direct effect on joint health by reduction of haemarthrosis [123]. The case series reported by Martin et al. (2017) investigated the efficacy of US-guided IA corticosteroid joint injection therapy in patients with haemarthropathy. In total 45 IA injections (14 ankles, 18 knees, and 13 elbows) were administered with reported reductions in pain VAS from seven to one ($P<0.001$) over 12 weeks. Participants with more radiological changes (higher Pettersson score) had a shorter therapeutic benefit, with 10-12 weeks of pain relief [151]. The use of corticosteroids may therefore provide the most benefit where synovitis is present and bone and cartilage damage is limited. This study concludes that the use of ultrasound (US) guided IA corticosteroid injections for haemarthropathy is a safe and clinically effective therapeutic intervention for pain [151]. No recommendations for IA corticosteroid injection are included in the UKHCDO guidelines, although the comment is made that in individual cases IA corticosteroid may provide short term symptomatic relief [43]. In a condition that requires regular rehabilitation and

management of chronic pain, these short term benefits may provide a window of opportunity to rehabilitate joints such as the ankle where pain and soft tissue fibrosis limit full rehabilitation.

2.3.2.2 Hyaluronan

Hyaluronan is a viscosupplementation where hyaluronic acid is administered by IA injection. Hyaluronan is used to restore the viscoelastic properties of the synovial fluid as well as change the disease process of the joint by stimulating synovium production of endogenous hyaluronic acid [108]. The effect of hyaluronan in OA and haemarthropathy is theoretical and it is thought to inhibit tissue nociceptors, stimulate the production of endogenous hyaluronan, anti-inflammatory and inhibit matrix metalloproteinase activity [152]. In a long-term follow-up study of 46 patients with haemarthropathy, affected joints were injected 3-5 times during a one to four week period. Improvement at six-month follow-up in VAS, joint function and QoL scores were reported in eight of 10 elbows, 15 of 24 knees, but the most improvement was observed at the ankle (22 of 25 joints). At the ankle, VAS scores were significantly reduced ($p<0.05$) compared to pre-intervention at six months (5.22 to 2.50), as were WFH Score (6.72 to 5.61), SF-36 (53.54 to 75.43) and ankle dorsiflexion (2.14° to 7.56°), but was not maintained at 12 months [153]. Caarulli *et al's.* (2013) follow-up study evaluated the long-term effect of IA hyaluronan over six years [152]. Participants with haemarthropathy of the knee (n=27) received a minimum of two injections over six years. Again, VAS, SF-36, ROM and WFH score improvements were observed at six months and up to 12 months, but as with the original study returned to the pre-injection state after 12 months [152]. Results suggest the use of hyaluronan may have benefit in the short-term management of ankle haemarthropathy but high-quality evidence is required to underpin universal adoption of hyaluronan use, However, the existing evidence provides insight into the potential benefits in early haemarthropathy and chronic joint disease, before surgery is indicated for joint pain management [108, 152].

2.3.2.3 Platelet-rich plasma

PRP is a high platelet-rich plasma concentrate containing high levels of growth factors that play a key role in the regeneration and stimulation of tissue healing, which includes cell proliferation, matrix remodelling and angiogenesis [154]. Two studies to date have investigated the effect of IA PRP in haemarthropathy [154, 155]. IA injection of PRP was followed up over a two to six month period. Caviglia *et al.* (2017) reported improvements in total HJHS from 15.750 (SD 0.729) to 9.786 (SD 0.671) over six months [154]. For the ankle, Vladimir & Bobek (2014) reported improvement of ankle HJHS from a pre-IA injection of 6.75 (3-12) and a reduction to 4.85 (1-10) after two month follow-up period [155]. Outcomes, confirmed with MRI, demonstrated a reduction in thickening of the synovial membrane and a dramatic decrease in joint effusion. MRI findings reported haemosiderin levels within the synovium did not change, and therefore the risk of future haemarthrosis complications may only be delayed. Pain measured by VAS (0-10) also improved from a mean of 5.57 pre-injection to 1.21 at three months and 0.64 at six months ($p<0.001$). In the shorter two month study by Vladimir & Bobek (2014), significant reductions of 0.75 ($P= \leq 0.0001$) between pre (2.85) and post (2.05) PRP were reported. In both studies, PRP reduces pain, with the largest effect reported at six months, but with small differences in pain reported over two months raises questions whether short term reductions in pain are clinically meaningful. Data on the minimal clinical important changes of pain in haemophilic synovitis of the ankle are yet to be established. In chronic MSK pain intensity, a VAS change of one has been associated with “slightly better” change and two as “much better” pain, therefore the significance of the VAS pain reduction of 0.75 should be interpreted with caution [156]. The use of PRP may provide potential therapeutic benefits in the short term management of synovitis, but based on current evidence is unlikely to become part of routine clinical practice.

2.3.3 Joint aspiration

The practice of aspirating blood products from a joint following intra-articular haemorrhage is thought to reduce the volume of haemoglobin within the joint, and therefore lessen the demands on the synovium and cartilage leading to an accelerated rehabilitation time [57]. Knee joint aspiration at 24 hours and up to five days post haemarthrosis are reported to make little difference to patient-reported pain, ROM and knee circumference when compared to a control group [157]. The author reported extreme pain and hypersensitivity of the knee during the procedure, where the joint capsule was very swollen and tight. The author was reluctant to recommend the procedure, concluding that aspiration in clinical practice would only be a consideration once the joint became lax or moderately swollen. More recently the UKHCDO recommend that aspiration should not routinely take place unless there is a suspicion of septic arthritis. Where pain does not subside aspiration may be considered but only with the correct haemostatic therapy cover [43].

2.3.4 Synovectomy

Synovectomy is a procedure performed in haemarthropathy to reduce the thickness of the synovial line of the joint by ablation, or surgical removal [158]. Reduction in this thickness leads to a reduction in the neovascularisation of the joint synovium and in effect “resetting” the joint. The ankle joint is a common site for synovectomy due to the high functioning nature of the joint [159].

2.3.4.1 Radioactive synovectomy

Radiosynoviorthesis or radioactive synovectomy refers to the restoration of synovia by the local application of a radiopharmaceutical agent which emits Beta-radiation [160]. Radioactive synovectomy is indicated to prevent the progression of haemarthropathy by restoring the synovial joint lining and reducing synovial hypertrophy [159]. Radioactive synovectomy offers long term benefits to haemarthrosis in target joints or those with

moderate synovitis, but several authors have raised concerns around the potential hazards [161-163]. Radioactive isotope leakage from the joint, subsequently causing soft tissue damage such as chromosomal changes and accumulation in other tissues such as lymph nodes is of concern [161, 163, 164]. Safety reports have identified incidence of isotope leak range from zero to 70% but without complications of malignancy [165]. A recent Canadian retrospective analysis of 2412 haemophilia and rheumatology patients who had undergone a radioactive synovectomy between 1976 and 2001 investigated the incidence of cancer. In both haemophilia and RA, the risk of cancer development was the same as the general population [163]. Recommendations for the most appropriate time to perform a radioactive synovectomy is yet to be standardised. Where haemophiliac synovitis is unresponsive to haematological treatment, a radioactive synovectomy is recommended as soon as possible and before radiological evidence of cartilage damage [43].

2.3.4.2 Surgical synovectomy

Reduction of synovitis by surgical approach is only indicated where there has been a failure of consecutive measures or radioactive synovectomy to halt haemarthrosis and reduce synovitis [166]. The surgical approach favours arthroscopy, by its nature is a less invasive approach. Open surgery is only undertaken when significant synovial tissue requires radical resection. Where advanced haemarthropathy leads to cartilage damage, subchondral cyst formation and arthritic changes, typically narrowing of the joint space, decreased joint ROM and pain make the effectiveness of radioactive synovectomy limited in its therapeutic benefit. At this stage, joint surgery is indicated [150, 166].

2.3.5 Ankle surgery in haemophilia

Where conservative, pharmacological and radiopharmaceutical measures cease to provide clinical benefit, surgical interventions are considered [8]. The main clinical presentations of ankle haemarthropathy are a gradual drift of the foot into plantarflexion,

soft tissue contracture, and gradual joint malalignment [53]. These structural and functional changes leading to osteophyte formation at joint margins, worsening ankle haemarthropathy and eventual chronic end-stage ankle haemarthropathy [150].

2.3.5.1 Joint sparing surgery

Surgical removal of the osteophytes formed on the posterior and anterior joint line is a potential surgical treatment where functional ankle dorsiflexion has been lost or increases the risk of haemarthrosis [8]. Worsening haemarthrosis occur which are identified by loss of dorsiflexion and increased patient-reported pain but in reality, by this stage, there is already significant cartilage bone damage and subchondral cyst formation limiting the benefit of the procedure [75]. In ankle OA, arthroscopic debridement of anterior ankle osteophytes, before the loss of joint space occurred, resulted in 90% excellent or good results. However, in patients with ankle joint space narrowing only 50% reported good results. In haemophilia, the clinical benefit is less clear. A review of ankle management by Rodriguez-Merchan [167] indicates the use of osteophyte debridement is a treatment option for patients with ankle haemarthropathy, however no detail of the procedure, PROMs or measures of function are reported.

2.3.5.2 Ankle replacement

The use of TAR as a treatment for ankle haemarthropathy demonstrates good pain relief, improved PROMs, and increase ankle function [168-170]. Traditionally haemophilia patients undergoing TAR between the second and third decades of life are at a higher risk of revision in later years. This has been attributed to increased rates of aseptic loosening, deep sepsis and long-term consequences of failure and revision surgery [8]. There is now emerging mid to long-term evidence that TAR may be a viable treatment option to reduce pain and retain a level of ankle function. In haemophilia adults with a mean age of 44 years (SD12) short to medium term outcomes (4.4 years, SD1.7, range 2.2-9.4), of TAR (n=32 ankles) report maintained improvements in pain, function and ankle alignment [171]. Similarly, medium to long term TAR follow-up (n=14), undertaken

by Eckers *et al.* (2018) over a mean of 9.6 years reported improvement in pain. Measured using VAS (0-10) patients reported pain levels of 2.9 with high levels of patient satisfaction and increased ankle ROM which improved on average by a mean of 10.2 (SD16.5) degrees (P=0.037) [172]. Systematic review and meta-analysis of long term TAR survival rates in (n=2239) have identified with non-haemophilic ankle OA TAR survival rates at 10 years of the median (95% confidence interval) 89% (95% CI 85 to 93). However annual failure rates of 3.2% (95% CI 2.0 to 4.4) [173]. The patients in Zaidi *et al*. (2013) study was a mean age of 60 which is higher than haemophilia TAR populations (43-44 years), and questions the longevity of TAR in ankle haemarthropathy. If failure rates in haemophilia are similar to the general population then patients may require conversion to ankle fusion at a much younger age, complicated by the loss of bone at the implant site and increased surgical risk, therefore it remains a selective treatment option [150].

2.3.5.3 Ankle fusion

Ankle fusion is the most common long-term treatment of chronic end-stage ankle haemarthropathy where conservative treatments have failed [8]. Incidence of talocrural joint fusion with subtalar joint fusion occurs in up to 26% of ankle fusion. Fusion of the subtalar joint in isolation is reported between 16 to 30% of cases [74, 76]. Longitudinal data of haemophilia patients who have undergone ankle fusion surgery (n=57) and followed up over a mean of 6.6 years (range 4 months to 20 years) report VAS of 0.75 (1.3SD) indicated that those with long-term fusion have low levels of pain [76]. Likewise, the American Orthopaedic Foot and Ankle Society (AOFAS) scores were 90.4 points (8.6SD) which represents a positive outcome (100 best score). In a similar study undertaken by Tsailas & Wiedel (2010), 20 ankle joints and subtalar (in isolation and together) joint fusions were followed up over a mean of 9.4 (range 1-18) years [74]. Again, an improvement in symptom scores (modified Mazur score) were reported with a symptom score of 94.9 (of 100) indicating excellent symptom outcomes. AOFAS scores

indicate a favourable functional outcome and support the use of fusion in the long-term treatment (>10 years) of end-stage ankle haemarthropathy.

Complications of ankle joint fusion in haemophilia occur due to post-operative bleeding, infection and the complication of HIV infection. In addition, non-union rates vary considerably with ankle fusion procedure failure rates in haemophilia reported as high as one in four and as low as one in 75 procedures [167, 174]. Functional consequences following fusion on the ankle joint in this patient group are not fully understood. The mechanical consequences of fusion and the additional non-surgical and non-pharmacological effect of postoperative management with devices, such as modified footwear, are yet to be investigated to determine the long-term effect that they have on patient-reported outcomes, proximal arthropathy of the knee and hip, and incidence of bleeding.

2.3.6 Orthotic devices and footwear

2.3.6.1 Foot orthoses

In-shoe orthoses, insoles, casted insoles, functional foot orthoses (FFO) stirrup and braces describe devices that exert, change or redistribute forces and pressures at the shoe-foot interface and stabilise the ankle joint in the presence of pathology [20, 108]. To provide clarity, the terms FFO and casted orthoses will be used to describe prefabricated and casted devices respectively in this section. Evidence supports the use of in-shoe casted orthoses and FFOs in the prevention of foot deformity and provides stabilisation in OA, IA and the management of the diabetic foot, but evidence for the management of ankle haemarthropathy is limited [17-20]. Review articles recommend the use of casted orthoses and FFOs in the management of ankle haemarthropathy, many of which refer to the use of orthoses as an adjunct to physical therapy but without any reported outcomes such as pain and functional changes [8, 21-25].

The effect of FFO on pain in patients with ankle haemarthropathy has been investigated [175]. Patients with haemophilia A (n=16) with varying levels of haemarthropathy received a set of casted orthoses made of polypropylene and four degrees rearfoot medial posting. Pre-intervention FFI scores were collected and repeated at a six weeks follow-up. Paired t-tests were used to analyse the two time points using the FFI subscales of pain, disability, activity and total FFI. Significant changes reported in pain ($p<0.05$) and overall disability/pain FFI ($P=<0.05$) index suggests casted orthoses are beneficial to people with haemophilia A, but in the absence of any clarification regarding the participant's severity (mild, moderate, severe), inhibitor status or treatment regime lessens the generalisability of the study findings. Those patients with less than 30 degrees of total ankle ROM were not included therefore excluding a large proportion of ankle haemarthropathy participants where up to 80% of ankle function is lost by the third decade of life [79]. Despite limitations in methodology, Slattery and Tinley (2001) reported a reduction in the incidence of bleeding in the study cohort. Findings represented not only the potential of casted orthoses as a non-pharmacological treatment but also represented significant cost saving in CFC treatment and significant benefit in participants QoL [158].

In the characterisation of rearfoot instabilities, Jorge *et al.* (2006) used plantar pressure measurement to quantify changes attributed to the use of FFOs in combination with airstrip devices and modified footwear to stabilise the ankle in the presence of haemarthropathy [176]. In-shoe plantar pressure analysis was used to observe changes in the centre of pressure (CoP) that have been reported in 43 haemophilia A and B patients with ankle haemarthropathy. Changes in the medial and lateral variance of CoP trajectory was reported indicating a more stable gait pattern with less variation in subtalar joint movement [177]. Kinematic 3D data was not collected in this study so it is unclear how reductions to the subtalar joint motion were attributed to CoP data only. In addition to the functional changes, FFO reduced ankle AJBR six months following use of the intervention. Unfortunately, as with Slattery & Tinley (2001) no analysis was performed

by Jorge *et al.* (2006) so it is unclear if functional and clinical changes were clinically significant, however less variation in CoP is a potential positive finding where haemarthropathy changes ankle and subtalar joint kinematics [175, 176]. The reduction of ABR and AJBR is often reported as an outcome in FFO intervention studies in people with haemophilia. Jorge *et al.* (2006) reported the reduction of spontaneous ABR in their total cohort; ABR reduced from 175 to 40 but traumatic ABR bleeds increased from 32 to 67 (P=0.004). The reasoning for increases in traumatic ABR has been reported in both studies and attributed to increased physical activity [175, 176]. The use of FFO alone may be counter-intuitive in people with haemophilia, therefore when activity increases the mechanical load on the ankle increases in pharmacological treatment may be required [178].

Tanaka *et al.* (1996) used similar casted orthoses constructed in 20mm EVA with a silicone heel cup to investigate whether the casted orthoses would be of clinical benefit to those with ankle haemarthropathy [179]. The casted orthoses were used in combination with modified footwear (11 participants) and elastic support (n=8), ankle-foot orthoses (AFO) (n=5) and above knee AFO (n=1). Allocation of the additional intervention was based on the severity of haemarthropathy and radiological scoring. Secondary outcomes consisted of the average frequency of haemarthrosis, ankle ROM, and X-ray imaging scored using a modified DePalma classification score, a haemophilia specific score of early (grade I) to late-stage (grade IV) joint pathology [180]. The use of casted orthoses did not affect activities such as walking or occupation and total ROM improved but without a significant change. A significant change in the frequency of haemarthrosis occurred when elastic supports were used; a mean of 4.0 (0.4 SE) to 1.8 (0.4 SE) bleeds per month ($p<0.05$) was reported. Interpretation of the results does not provide any insight into the use of casted orthoses in haemophilia. The use of a validated PROM may have provided further insight. The variation of interventions used (casted orthoses AFO, footwear modification) limit the ability to provide any insight into a specific intervention effect. The significance of reductions in the frequency of ankle

haemarthrosis suggests that casted orthoses in combination with elastic supports and modified shoes reduce ankle haemarthrosis. In addition to their orthotic interventions, patients and parents received education on CFC infusion, prophylaxis regime (interval of treatment) and changes to CFC dose in patients who had an increase in the frequency of ankle haemarthrosis suggesting that the reduced frequency of haemarthrosis may be a result of improved treatment regimens and maintenance of haemostasis confounding results [179].

The effect of AFOs on unilateral ankle pain in haemophilia has been investigated by Oleson *et al.* (2017) [181]. Participants with haemarthropathy were recruited to compare two different ankle supports (fracture boot & Carbon fibre AFO) for a reduction in ankle pain when compared to the unaffected limb (within-participant comparison) wearing a standard trainer. Temporal and spatial parameters and an 11-point numerical pain rating scale (NPRS) were used to assess function and pain. NPRS was significantly reduced when both devices were compared to a standard shoe ($p<0.05$), with no brace scoring 2.71 (0.47 SE), fracture boot (1.26 SE) and the carbon fibre 1.09 (0.32 SE). However, no difference was detected between conditions (fracture boot & Carbon fibre AFO). The fracture boot significantly ($p<0.05$) increased step time, cycle time, and swing time when compared to non-brace conditions [181]. Reported differences in pain, whilst significant provided little insight into the effect on pain, as there is no minimally important difference to challenge the significance of pain change. Both devices show potential in the management of ankle haemarthropathy and may be more appropriate at the chronic stages of haemarthropathy where stabilisation of the ankle joint has the potential to reduce pain. Likewise in the early stages of joint haemarthrosis, immobilisation with prefabricated AFO may provide a splinting action. Further investigation with larger cohorts and more sophisticated measures of gait, such as 3D gait analysis, and health-related QoL outcomes may provide insight into the mechanical effect of the intervention and the gains in QoL where function is impeded and QoL is impacted by pain [8, 182].

Few studies have investigated the kinetic and kinematic effect of orthoses in haemophilia and haemarthropathy. Lobet *et al.* (2012) explored the functional impact of casted orthoses used in combination with standard and orthopaedic shoes [14]. A cohort of adults (n=16) with ankle haemarthropathy was compared at baseline and a mean follow-up of 17 (+/-5) weeks. Changes were reported for external foot progression of 3.1 degrees ($p<0.001$), an increase of 0.32 W kg^{-1} ($P=0.004$) in peak concentric power during the push-off phase of gait. The improvements in external rotation and foot abduction represent a potential correction of compensatory mechanisms such as foot pronation that allows the body to progress over the foot during stance in pathological gait [183]. The correction of the frontal plane composition may therefore allow a more linear contraction of the gastrocnemius and soleus complex with improvement in peak concentric power, but the lack of foot and ankle kinetic and kinematic data limits any firm conclusion. FFI-R scores were not significant between conditions, only the subscale of pain decreased by nine points in those patients who were satisfied with their casted orthoses. Overall, the biomechanical impact between those who were satisfied/ not satisfied with their casted orthoses was similar [14].

Several review papers have reported the use of foot orthoses in the management of haemophilia. More specifically changes associated with ankle haemarthrosis, pain, physical impairment, changes in the axis of ankle joint, and as an aid to rehabilitation [150, 184, 185]. The use of silicone heel cups, whilst not a true orthotic device, does have the potential to change lower limb biomechanics. Seuser *et al.* (1997) found the silicone heel cup caused instability at the ankle joint, though no reasoning for this conclusion was provided [186]. In clinical practice, the soft silicone heel cups typically deform rapidly under load, and therefore would not be a treatment choice for the management of ankle pathology due to the potential to decrease stability at heel loading. There is potential for increased variability in front and sagittal plane ROM and therefore increase the risk of soft tissue trauma and pain, but this was not reported. A combined approach to the provision of foot orthoses and footwear have produced significant

reductions in patient-reported pain and disability, with excellent patient satisfaction [15]. The combined clinical benefit of FFO and footwear are yet to be established in ankle haemarthropathy. Research to date lacks the methodological design to ascertain the true mechanical effect of the interventions in part as they have been used with other devices such as ankle braces. Several review articles include the use of orthotic devices, but lack clarity in their application, often including the intervention as an adjunct to physical therapy and appropriate CFC therapy.

2.3.6.2 Footwear

When the anatomical rocker mechanism is impeded by pathological changes, modified footwear may substitute the ankle rocker at heel strike, through to toe-off during the stance phase of the gait cycle [187, 188]. Modified footwear is commonly used in the management of conditions such as diabetes and RA, to prevent ulceration and improve mobility and function in several conditions associated with impaired walking and orthopaedic deformity [188-190].

Rocker profile shoes and solid ankle cushioned heels (SACH) are regarded as two of the most common footwear modifications [191]. The majority of research on rocker profile footwear concentrates on the offloading and redistribution of pressure associated with the occurrence of diabetic foot ulceration [188]. In ankle haemarthropathy, a rocker profile shoe has the potential to compensate for the reduction in ankle ROM by providing a mechanism for the body's centre of mass to progress over the foot during the stance phase [188]. A heel-toe rocker whereby a negative heel rocker is used in combination with a forefoot rocker has been suggested as the most appropriate configuration in the presence of ankle OA or where ankle ROM is impeded [188, 192]. A double rocker sole has been shown to decrease plantarflexion moment at midstance through to toe-off with an increase of dorsiflexion ROM at MS [187]. A decrease in dorsiflexion was also seen at the late stance phase and initial swing phase whilst maintaining normal walking speed when compared to a normal shoe in healthy adults (n=40) [187]. A smaller study (n=17)

of healthy control participants by Arazpour *et al.* (2013) also reported a reduction in terminal stance timings [187, 193]. The use of a heel-toe rocker shoe similar to the shoe used by Long *et al.* (2007) increased dorsiflexion by 9.2° when compared to a standard shoe. Both studies support the use of a double rocker, or heel-toe rocker in the management of ankle OA and arthrodesis but at the sacrifice of frontal plane motion that increased in both studies. Long *et al.* (2007) reported a decrease in loading at midstance that could not be accounted for due to movement of the foot within the shoe between footwear conditions (standard and rocker) that cannot be measured by shoe-mounted markers [187]. Arazpour *et el.* (2013) found a significant increase (p 0.023) in inversion and eversion angles during second double limb support between standard shoe (16.8°, SD 4.8) and rocker (26.8, SD 4.4) conditions [193]. Whilst the findings are positive, true estimates of ROM are not captured by the biomechanical methods used and therefore rearfoot frontal plane ROM may be under-reported as the foot moves within the shoe. The study used two different footwear types, and no analysis of the carryover effect was performed which may have affected results if a period of adaptation to the footwear condition was not observed. To date, no follow-up study has been performed in patients with ankle arthrodesis so it remains to be seen whether findings translate to pathological ankle disease. The findings from both studies highlight the potential benefit of footwear to manage biomechanical changes at the ankle joint. Therefore application of footwear modification to ankle haemarthropathy cohorts warrant further investigation [187, 188, 193].

Originally designed for use in amputees and prosthetics, the SACH modification is designed to allow a normal heel strike during the stance phase of gait. When applied to footwear, a SACH creates a pseudo-plantarflexion moment by deformation underload forces and is made of a material softer than that of a solid sole unit. Wu *et al.* (2004) observed the effect of a “spongy” SACH modification in combination with a forefoot rocker at 60% of a shoe [194]. During level walking participants experienced increase dorsiflexion/plantarflexion at the hindfoot in relation to the tibia (30.2° (5.9°SD) vs 24.2°

(3.0°SD)) when compared to a traditional shoe. The addition of the rocker profile at the forefoot only decreased ROM when compared to a forefoot and hindfoot (18.4° (6.3°SD) 30.1° (4.6°SD) rocker. The effect of SACH has been suggested to produce a pseudo plantarflexion moment rather than a kinematic effect, therefore reporting of ankle kinematics may have been strengthened by the reporting of ankle kinetics [192]. Rapid heel to toe movement with an increase in varus and valgus angles was reported at the rearfoot, with a total 5° increase in ROM may suggest the material used in the spongy SACH deformed too rapidly underload. Participants suggested the SACH did not provide enough cushioning, nor did it feel thick enough. More detail on the material may provide more insight into the condition, but suggests a material that gradually deforms may be more suitable.

To date, there is little empirical evidence to support changes in practice, or management guidelines [14]. No research study has been undertaken in haemophilia to understand the mechanical effect of modified footwear in people with haemophilia. Therefore the mechanical benefit of such modifications in conjunction with in-shoe orthoses must be undertaken in ankle haemarthropathy before findings become part of standard clinical practice in comprehensive haemophilia care.

2.4 Health-related quality of life

The literature presented in section 2.4 provides an overview of health-related QoL (HRQoL) measures, patient-reported outcome measures and joint heath measures. Further detail in the relevant sections of chapter four titled (The impact of blood induced ankle arthritis in patients with moderate and severe haemophilia A and B: The HAPII study).

The physical burden of haemophilia and haemarthropathy is significant. HRQoL or the measure of the mental and physical burden provide a deeper understanding of a patient's QoL [195]. Those with severe haemophilia report worse QoL when compared to moderate and mild haemophilia and the general population. HRQoL differences have been reported to decline in haemophilia dependant on the severity of the disease [11]. Moderate haemophilia is associated with less burden, less physical limitation and therefore patients typically report better HRQoL than those with severe disease, but worse than those with mild disease [196]. Changes in joint status caused by haemarthrosis and haemarthropathy are a significant contributor to the burden of haemophilia and the associated effect of HRQoL [197]. In a cohort of 381 American patients with severe to mild haemophilia, Kempton *et al.* (2017) investigated the reliability of PROMs in the assessment of pain and functional impairment. Adults with a history of haemarthrosis, and joint pain, and in a non-bleed steady-state were assessed using PROMs, joint ROM and concurrent HJHS scores [10]. Median (IQR) SF-36 were lower for the physical domains of physical function (44.4 (29.7-52.8)) physical health (39.2 (29.5, 49.4)) and body pain (41.8 (37.2, 51.1)). The author also reported participant problems with mobility, usual activities and pain/discomfort subscales of the EQ-5D-5L increased. However, only the EQ-VAS (0-100 best health) of 80.0 (66.0, 90.0) were reported which indicates patients perceived their health status was generally good despite chronic pain and correlate with a similar evaluation of pain in haemophilia [198]. This study provides detail of the effect of joint pain and functional limitation on HRQoL in patients with a history of haemarthrosis. The ankle, identified as the most painful joint,

accounted for 37.4% of patients most painful joints, followed by the knees (23.7%) and elbows (18.9%), although HJHS (v2.1) scores did not differ significantly (4.0, 4.0 and 6.0, respectively). This study was performed in the USA where a private healthcare model differs to that of the UK NHS, but patients still receive the same levels of CFC under the comprehensive care model [199]. Regardless, those on treatment who were classed as "steady or not bleeding", still reported reduced HRQoL, low HJHS scores but a higher incidence of pain. Understanding how haemarthrosis and haemarthropathy of the ankle contribute to overall health may provide further insight to the HRQoL. Use of a disease specific and region specific QoL outcome measures may provide information of the contribution ankle pathology have in modern haemophilia treatment. To date, no study has evaluated the impact of ankle haemarthrosis and haemarthropathy on the HRQoL in those with moderate and severe haemophilia A and B.

2.4.1 Outcome measures

2.4.1.1 Haemo-QoL-A

The HAEMO-Qol-A is an HRQoL score developed by consensus agreement to measure the QoL in adults with haemophilia. Originally developed for use in the paediatric population (Haem-Qol) the HAEMO-Qol-A was adapted through the agreement of an international group conducted across multiple sites (USA, Canada, Germany and Spain) [200]. The HRQoL measure is made up of 41 questions and scored by subscales of physical function, role function, worry, consequences of bleeding, emotional impact and treatment concern [201]. Each of the 41 questions is scored on a six-point Likert-type scale ranging from 0 (None of the time) to 5 (All of the time). A higher score indicates a better HRQoL or less impairment of that particular subscale or raw scores can be combined to produce a total score (0-100) [200]. The HAEMO-Qol-A has shown good internal consistency (Cronbach's a 0.95) and reliability for each subscale and overall total scores over a four-week period. Field validation results strongly supported the use of the HAEMO-QoL-A as a clinical and research PROM. Systematic reviews of outcome

measures in haemophilia have identified that the HAEMO-QoL-A has strong content validity but only moderate evidence of cross-cultural validity [202, 203]. When compared to the generic QoL measure of the SF-36, the HAEMO-QoL-A displayed moderate to strong correlation, with pain, social function and role limitations displaying the largest correlations with the SF-36 [200]. Whilst limitations in test-retest reliability and hypothesis testing of the HRQoL measure have been identified, the HAEMO-QoL-A is the most widely used and clinical validated measure of HRQoL in haemophilia [202, 203].

2.4.1.2 Haemophilia health joint status (HJHS)

The HJHS is an internationally developed and standard assessment tool in haemophilia comprehensive care. Developed by the International Prophylaxis Study Group, the HJHS was aimed at providing a standardised clinical tool for identifying changes in joint function in haemophilia for children and later adapted for young adults (14-30 years) on prophylaxis factor replacement therapy evolving over three versions to its most recent version 2.1 [204, 205]. The HJHS evaluates upper and lower limb joint swelling, duration of joint swelling, axial alignment, muscle atrophy, crepitus and active ROM [206]. Reliability of the HJHS inter-rated and retest reliability has been undertaken in eight haemophilia children (4-18 years). ICC overall inter-rater reliability was good (ICC=0.83) as was the intra-rater reliability (ICC 0.89) [204]. When compared to the WFH produced Gilbert score, the HJHS provided better sensitivity to early arthropathic changes. The use of the HJHS may be limited in developing countries where factor treatment is not available, or the burden of haemarthropathy is greater and access to medical professionals is limited [203, 204]. Regardless, the HJHS is adopted globally, adapted in several different languages and used frequently as a clinical outcome measure in pharmacological and clinical research [204, 207]. Whilst there is some discussion about its sensitivity in the early stages of arthropathic changes, the accumulative nature of the score provides insight into individual and total joint health, but the HJHS is yet to be validated in adults (>30 years) who have more established arthropathy [79, 208].

The HJHS ability to measure joint health in early and late-stage haemarthropathy has undergone sensitivity analysis to detect soft tissue and structural joint changes when compared to radiological modalities (X-ray, MRI, US). In severe haemophilia and von Willebrand's disease good correlation has been reported in adolescence (15 years, 5-17) with haemarthropathy (n=51) of varying levels of arthropathy measured by the Pettersson radiological score [209]. Good correlation was reported between the Pettersson score and HJHS (r_s =0.66), and at the knee (r_s = 0.75: 95% CI (0.58 to 0.85) but only moderate correlation with the ankle joint [r_s = 0.49: 95% CI (0.28 to 0.66)]. Therefore the HJHS may under-report actual ankle joint changes. When compared to MRI and US, the HJHS was unable to identify pathological changes in joints that appeared normal, but as the pathological state deteriorates, the HJHS may provide more information in combination with radiographs. Poonnoose *et al.* (2016) concluded that knee and ankle HJHS of less than three or 'near normal' joints may require the use of additional US or MR imaging to determine arthropathic changes [209]. Where haemarthropathy becomes more advanced, the use of the HJHS and radiographs becomes more informative. Although limitations have been identified in ankle scores, it is still the most widely used clinical score of joint health and currently, the HJHS score is a clinical treatment requirement for all UK registered severe haemophilia A and B patients for both children and adults with severe haemophilia [13].

2.4.1.3 Foot and ankle patient outcome measures

Whilst disease-specific and general QoL measures provide insight into current disease, region-specific outcome measures allow the evaluation of the effect on specific MSK areas such as the ankle and foot [210]. To date, only three measures of foot pain have been used in clinical studies and service evaluation of haemarthropathy treatment and management. The Manchester foot pain and disability index, FFI and the foot FFI-R short form have been used to report differences in treatment and intervention studies [15, 19, 175]. Whilst all three PROMs are frequently used to measure foot pain, function, psychosocial and QoL, in a condition characterised by haemarthrosis of the ankle joint,

the language used i.e. foot pain may limit its use in understanding ankle pain and disability. In clinical practice, patients distinguish foot pain and ankle pain as two separate entities, therefore using PROMs that are specific to the ankle haemarthropathy may provide more accurate information to ankle outcomes [211, 212]. The Manchester–Oxford Foot Questionnaire (MOXFQ) (foot and ankle) was developed as an outcome of foot and ankle surgery and more recently used in clinical trials of interventions such as orthoses [213, 214]. The MOXFQ is a patient questionnaire consisting of 16-items related to walking/standing, social interaction and pain, of the foot and later adapted to include ankles (pain in your foot/ ankle) [214]. MOXFQ consist of three domains, walking/standing (seven questions), pain (five questions) and social interactions (four questions).

Evaluation of an index or total score created from the subscales of the MOXFQ yielded greater precision when compared to the SF-36. Measurement properties of the MOXFQ, originally tested in relationship to hallux valgus surgery performed well in patients undergoing surgery and when compared to the generic 36-item Short Form Survey (SF-36) and AOFAS [215]. Pre and 12-month postoperative scores of the outcome measures identified that the MOXFQ effect size was greater than those obtained from the SF-36 and AOFAS, with satisfactory to optimal Cronbach's alpha (>0.7, range 0.80-0.90) representing internal validity of all MOXFQ subscales. Whilst the MOXFQ was constructed of the three domains of walking/ standing, pain and social interaction a summary score has been produced more recently to provide a single index measure that reports an overall indication of the foot and ankle outcome [213]. The reliability of the summary score assessed using Cronbach's alpha was high (0.93) indicating internal consistency of the three domains. Similarly, when compared to the SF-36 the summary score attained moderate correlations (R* 0.34 to 0.70) with the relevant domains (physical function, role physical, social function and energy/vitality) all of which were clinically and statistically significant (P=<0.001) in the evaluation of overall impact and support the validity of the index scores use. The findings of Morley *et al*. (2013) therefore

support the validity of the index score in the assessment of the impact of foot and ankle disease. The MOXFQ has been validated and widely used as a pre and post PROM of foot and ankle surgery and more recently conservative intervention studies including ankle-foot orthoses (AFO) [216]. In addition, the MOXFQ has been converted to multiple languages and cross-cultural validation has been undertaken [217-219]. A recent systematic review that investigated the measurement of PROMs in foot and ankle disease concluded that the MOXFQ had the best overall, psychometric properties, internal consistency, reliability, measurement error, structural, convergent, discriminant, discriminative validity and responsiveness [220].

The MOXFQ is yet to be utilised in haemophilia clinical practice or research, but the addition of the term ankle in questionnaire construct (pain in ankle/foot) lends itself to a condition where pathology is predominantly the talocrural joint such as ankle haemarthropathy.

2.5 Summary

Haemophilia is an X-linked recessive genetic disorder characterised by bleeding into soft tissue and joints. In those with severe and moderate haemophilia CFC is used to halt or reduce the risk of spontaneous and traumatic bleeding. Whilst prophylaxis has decreased the burden of haemarthropathy, treatment is still sub-optimal across European countries. Bleeding within the MSK system accounts for 90% of all bleed incidents in haemophilia, with the ankle to date the most commonly affected joint, previously identified as being the site for 20% of all MSK bleeds. The high incidence of ankle haemarthropathy and changes to structure and function of the ankle joint can be attributed to episodes of haemarthrosis. Changes to the joint initiated by synovitis, synovial hypertrophy, cartilage, and bone damage lead to structural changes that can result in loss of 80% ROM at the ankle by the third decade of life with significant patient-reported pain and disability. Despite this, the true prevalence and impact of ankle haemarthrosis and haemarthropathy are yet to be established. The structural and

functional changes to the ankle joint result in pathological biomechanical changes in the lower limbs. Footwear and functional foot orthoses have the potential to change patient HRQoL, pain and disability but to date, there has been limited research of significant academic quality to inform practice or change clinical guidelines. Orthotic devices such as FFO and modified footwear have the potential to reduce the burden of ankle haemarthropathy. Research to date is limited by methodological design and inadequate sample sizes. Methods of functional analysis, such as kinetic and kinematic data collection have become more sophisticated allowing more subtle understanding. Investigating the mechanism of action of these interventions is required before wider use in the haemophilia population.

Understanding the prevalence, impact of ankle haemarthrosis in moderate and severe haemophilia will lead to a better understanding of the condition. Establishing the mechanism of action of a potential intervention will enable future research and targeted intervention in the management of ankle haemarthropathy.

Chapter 3 - The prevalence of ankle haemarthrosis in moderate and severe haemophilia A and B

This chapter describes the prevalence of ankle haemarthrosis in the UK adult population. Data were obtained from the UKHCDO national haemophilia data analysis group to establish the prevalence of haemarthrosis and levels of concurrent haemarthropathy at the ankle and other commonly affected joints. The pathological process of haemarthropathy has been discussed in the chapter two literature review, therefore this introduction will provide a brief background of haemarthrosis and the current UK and European trends.

3.1 Introduction

Haemarthrosis is an inherent clinical feature of severe haemophilia, a disease characterised by spontaneous and traumatic bleeding. Musculoskeletal bleeding is the most common haemorrhagic manifestation of severe haemophilia, with 90% of bleeds occurring in muscles or joints [1]. The presence of blood products within the joint space and the process of removal leads to synovial hypertrophy, haemosiderin deposition and eventual arthropathic joint changes [46]. Over time the biological burden of repeated haemarthrosis results in changes to cartilage, bone composition and progressive chronic haemarthropathy [3, 4]. In joints, including the ankle, changes to the structures caused by haemarthropathy inhibit joint function and are particularly prone to re-bleeding [59, 60]. The resultant haemarthropathy of affected joints is a cause of significant pain, disability and detriment to health-related quality of life (HRQoL) [44, 46].

Regular treatment with replacement or bypassing clotting factor concentrates (CFC) are termed prophylaxis [1]. The aim is to maintain a factor level or equivalent (bypassing products) that halts spontaneous and traumatic incidence of bleeding. Primary prophylaxis with CFC are the treatment regime of choice in the developed world and form part of the treatment guidelines for the UKHCDO and World federation haemophilia

[31, 221]. Standard factor treatment is effective at decreasing the frequency of bleeding. Evidence in young children has shown that prophylaxis is effective at the prevention of joint damage and bleeding events, but does not protect against all incidences of bleeding [32-34]. Traditionally, prophylactic treatment in severe haemophilia aims to maintain factor VIII (FVIII) or Factor IX (FIX) at a trough level >0.01 IU/ml. It is apparent that many patients experience spontaneous as well as traumatic bleeds despite achieving trough factor levels > 0.01 IU/ml. In recent years treatment options have improved dramatically with the development of personalised treatment regimens with standard half-life (SHL) products. Specialist laboratory testing and pharmacokinetic (PK) profiling has also been shown to effectively predict CFC treatment effect and individual half-life profiles. PK profiling, therefore, models the derogation of clotting factors and change dosing and frequency [222, 223]. For example, if treatment is taken at night levels may drop to a level that increases the risk of bleeding such as exercise or work-related activities the following afternoon. Extended half-life products (EHL) have similarly been shown to maintain trough levels by 1.6 to 1.8 times SHL products, but the treatment is yet to definitively improve outcomes [49, 224-226].

Primary prophylaxis, the treatment of children for those age three years, without clinically detectable joint damage was not a treatment option for many older adults with haemophilia. Subsequent mistrust of treatment caused by contaminated blood products meant those individuals adopted on-demand treatment by preference or only when deemed necessary [227]. The introduction of recombinant clotting factor concentrates, a synthetic (recombinant) factor replacement product and reduced treatment burden (fewer infusions) have seen increased uptake in prophylaxis in older children and adults, defined as secondary prophylaxis but multi-joint haemarthropathy is often a common feature in this group [228]. In the presence of established haemarthropathy Collins *et al*. (2010) investigated the efficacy and safety of secondary prophylaxis in adults aged 30-45 years with severe haemophilia A. The authors reported a treatment dose of 20-40 IU kg^{-1} three times per week led to a significant reduction in the incidence of haemarthrosis.

Annual bleed rate (ABR) reductions and improvements in health-related QoL were significant when compared to on-demand treatment. Whilst joint health stabilised no definitive conclusions on the effect on joint health could be reported, but appropriately dosed secondary prophylaxis treatment regimens are clearly beneficial were haemarthropathy is present [2, 49].

Evaluation of real-world clinical treatment regimes in severe and moderate haemophilia in the UK and Europe, have shown that despite adequate CFC availability, treatment is still suboptimal. In 2015, data from the United Kingdom National Haemophilia Database (NHD) reported median (IQR) ABR/ annualised joint bleed rates (AJBR) in children (0-11y) and adolescents (12-18y) of 1.0 (0.0-0.5)/ 0.0 (0.0-1.0) and 2.0 (0.0-7.0)/ 1.0 (0.0-3.0), respectively. ABR in adults with severe haemophilia A on prophylaxis were 2.0 (IQR 0.0-7.0) and AJBR were 1.0 (IQR 0.0-4.0) with only 29% bleed free and 34% joint bleed free [4]. Similarly, European (Belgium, France, Germany, Italy, Spain, Sweden, and the UK) data shows a median AJBR of 1.0 – 4.0. [3, 4]. However, data on the bleed frequency and severity of haemarthropathy at an individual joint level is lacking. Likewise, the reporting of Haemophilia Joint Health Score (HJHS) lacks the specificity to identify the clinical impact on individual joint health and disability, especially the ankles that are often more problematic [9, 18].

The main sites of haemarthrosis are the elbows, ankles and knees, with the shoulders, wrists and hips less common affected and therefore not collated by the NHD or recorded as part of the HJHS [9, 206]. The ankle has previously been cited as the most common site of haemarthrosis in boys with severe haemophilia A and continues to be identified as a problematic joint in the physical and pharmacological management of haemophilia [9, 229]. The increased uptake of prophylaxis and new emerging treatments means the prevalence of joint haemarthrosis, and incidence at each joint and joint health status of interest is unknown. This study, therefore, aims to establish the current prevalence and incidence of ankle joint haemarthrosis and its relationship to other commonly affected

joints of the musculoskeletal system. Understanding the distribution, incidence and prevalence of haemarthrosis and joint health in adults deemed compliant with prophylaxis may provide direction for future pharmacological research and targeted interventions; including non-pharmacological interventions and intra-articular therapies commonly used in the management of MSK conditions.

3.2 Aims

This study aimed to identify the current prevalence and incidence of haemarthrosis in the ankle and other commonly affected joints in adults with moderate and severe haemophilia A and B. In addition, this study aimed to explore total and individual HJHS a clinical measure of joint structure and function, therefore impact on the MSK system. Exploration of the HJHS in combination with AJBR data will provide the current prevalence and incidence of ankle haemarthrosis and the clinical impact on joint health in the adult moderate and severe haemophilia population.

The specific aims of this study are as follows

I. To establish the prevalence and incidence of ankle haemarthrosis in adults with moderate and severe haemophilia by obtaining UKHCDO, NHD data from those deemed Haemtrack compliant.
II. To compare prevalence and incidence of ankle haemarthrosis to other commonly affected joints of the musculoskeletal system.
III. To report HJHS concurrent joint health, the severity of haemarthropathy at the ankle and other reported joints.

3.3 Participants and Methods

Ethical approval was obtained on 24th January 2017 (IRAS: 206141, R&D: PD16/227) as part of the HAPII study investigating the prevalence and impact of ankle haemarthrosis in severe and moderate haemophilia (Chapter Four). Once ethical approval had been obtained, the application was submitted to the NHD Data Analysis

Group to obtain NHD data. The application was considered on 14th June 2019, with approval granted on the 12th of July 2019. Data were requested from all adult patients (≥18 years) with severe (<0.01 IU/mL) and moderate (≥0.01, <0.05IU/mL) inhibitor and non-inhibitor status with haemophilia A and B registered in 2018. Data from people with moderate haemophilia did not meet the required numbers of participants for inclusion and were subsequently excluded from the report.

prevalence, incidence and joint site data were collated retrospectively from Haemtrack and HJHS from the NHD. Therefore, data were reported in adults aged 18 years and above with severe haemophilia A and B (FVIII or FIX <0.01 IU/mL) without a current inhibitor, issued with CFC in the UK between the 1st January and 31st December 2018. Regular prophylaxis was defined for those using standard half-life (SHL) prophylaxis as >=2 infusions per week for Haemophilia A, and >=1 infusions/week for haemophilia B. For those using extended half-life (EHL) products, regular prophylaxis was defined as >=1 infusions/week for haemophilia A, and >=1 infusion every two weeks for haemophilia B for >45 weeks/year. Those included in the analysis were Haemtrack compliant (defined as recorded use of ≥75% of received CFC) with a corresponding electronically recorded HJHS Version 2.1. Haemtrack is a UK national online treatment diary whereby individual patients regularly report details of treatments with CFC, including the reason for each treatment such as prophylaxis or bleed treatment and the site of each bleed [230, 231]. The online diary records data on CFC delivered or collected from a patients comprehensive care centre (CCC) or haemophilia treatment centre (HC). Once clotting factor concentrates have been administered the patient should then record that particular treatment episode using the Haemtrack app or website. The most recent UKHCDO bleeding statistics report 2018-2019 reported median compliance at CCC and HC of 90% and 93% respectively [232]. Whilst the compliance of record-keeping varies by patient and centre the NHD require patient treatment delivered, or collected by the patient CCC and HC. Treatment is recorded by a data manager for each CCC/HC, and uploaded to the NHD quarterly. When the treatment has been self-administered by the patient they

are then required to report each individual episode on Haemtrack. A >75% threshold of treatment delivered or collected vs administered by the patient as the minimum inclusion criteria and therefore available for data analysis [4, 231]. Data recorded in Haemtrack are then integrated with NHD. Data is monitored to ensure the safety of treatment such as ineffective treatment, or complications such as inhibitor development at the individual centre and national level. The NHD use data to improve the care of patients with bleeding disorders, NHS clinical treatment services and provide data that informs treatment funding and safety [230].

The HJHS is used globally as a measure of joint health status in patients with severe haemophilia and the UKHCDO haemophilia management guidelines recommend that this is completed every 6-12 months [204, 233]. The HJHS is a standardised clinical assessment tool developed to evaluate upper and lower limb joint health and status [204]. Measures include joint swelling, alignment, range of motion, muscle atrophy and crepitus; it has shown good inter-rater (ICC=0.83) and intra-related (ICC=0.89) related reliability in children and young adults [205, 206, 220]. In the prediction of joint status, the HJHS has shown a correlation with Pettersson radiological scores. Correlation is reported as good at the knee (r_s = 0.75: 95% CI (0.58-0.85) but only moderate with the ankle joint (r_s 0.49: 95% CI (0.28 – 0.66) [209]. Whilst limitations have been identified in ankle scores, the HJHS is yet to be validated in adults (>30 years) but it is the most widely used score of joint health in haemophilia. The HJHS Version 2.1 is collated as six individual joint scores (0-20) and compiled with a global gait score (0-4) to a total score (0-124), with higher HJHS representing worse joint health. Workshops have been conducted in the UK to decrease inter-centre variability in HJHS scoring. Where HJHS is recorded electronically by the local haemophilia centre, it is available to the NHD to analyse and uploaded by a local data manager at CCC and HC. The prevalence of joint bleeding was determined by the proportion of patients who reported haemarthrosis over the 12 month study period. The incidence of new episodes of haemarthrosis at each joint over the 12-month study period was captured by the AJBR. Joint bleed prevalence (%)

for adult patients AJBR incidence and HJHS were collated from Haemtrack and NHD. Joint bleed prevalence, AJBR and HJHS are reported for all joints (total) and in each joint.

3.4 Analysis

Analyses were undertaken by the NHD and a descriptive summary was produced as per the NHD data reporting process. Data presented describes adult males (≥18 years) with severe haemophilia A and B (FVIII or FIX <0.01 IU/mL) without a current inhibitor issued with CFC between 1st January and the 31st December 2018. Participants were Haemtrack compliant and had fully itemised HJHS during the study period. Data were summarized by mean, standard deviation (SD) median, and interquartile range (IQR, 25-75 percentiles) with age calculated at the midpoint of the study period. The primary outcome of this study was haemarthrosis prevalence [n (%)]. AJBR incidence and HJHS were reported for all joints as a total score (total), and at an individual joint level (ankle, knee and elbow) by side (left/right).

3.5 Results

During 2018, 2338 individuals with severe haemophilia A (n=1889) and B (n=349) without a current inhibitor were registered with the NHD and 1396 were registered with Haemtrack. Simultaneous Haemtrack and electronically recorded fully itemised HJHS data were available for 273 of which 176 individuals were adults (Table 1). 86.81% (n=157) of the sample were patients with haemophilia A and 13.19% (n=19) were patients with haemophilia B. Median (IQR) age in the haemophilia A sample was 40 (29; 50) and haemophilia B was 45 (25; 48) years.

Prophylaxis compliance as defined in section 3.1 was high, with 96% of haemophilia A and all haemophilia B patients compliant with their individual treatment regime. Treatment characteristics of those sampled using SHL and EHL products report that in haemophilia A 23% (n=36) of adults used an EHL product and during the 12-month study

duration 4% (n=6) switched from an SHL to EHL product with the remained treated by SHL products (73%, n=115). In the cohort of Haemophilia B patients, 42% (n=8) used an EHL product, 26% (n=5) switched from an SHL to an EHL product and the remainder were treated with an SHL product (32%, n=6).

3.5.1 Joint bleed prevalence and annualised bleed rate

The combined total of joint bleed prevalence and AJBR and incidence by the site (Ankle, knee, and elbow) and side (left and right) are presented in Table 1 by haemophilia type (A and B). In this study prevalence of 59.9% and 42.1% were reported in haemophilia A and B respectively, reporting at least one bleed over the 12 month study period. Combined AJBR incidence is presented in Table 1 indicating ankles are the most frequent site of haemarthrosis.

Table 1: Annual joint bleed prevalence and AJBR				
Joint			Haemophilia A (n=157)	Haemophilia B (n=19)
All Joints	Joint bleed prevalence	n (%)	94 (59.9)	8 (42.1)
	Annual joint bleed Rate	Mean (SD)	3.90 (7.00)	2.04 (3.59)
		Median (IQR)	1.0 (0.0;4.4)	0.0 (0.0;3.5)
Right Ankle	Joint bleed prevalence	n (%)	27 (17.2)	2 (10.5)
	Annual joint bleed Rate	Mean (SD)	0.38 (1.06)	0.16 (0.51)
		Median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
Left ankle	Joint bleed prevalence	n (%)	35 (22.3)	2 (10.5)
	Annual joint bleed Rate	Mean (SD)	0.61 (1.98)	0.11 (0.33)
		Median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
Right knee	Joint bleed prevalence	n (%)	27 (17.2)	2 (10.5)
	Annual joint bleed Rate	Mean (SD)	0.41 (1.48)	0.53 (2.08)
		Median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
Left knee	Joint bleed prevalence	n (%)	24 (15.3)	2 (10.5)
	Annual joint bleed Rate	Mean (SD)	0.29 (0.96)	0.21 (0.72)
		Median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
Right elbow	Joint bleed prevalence	n (%)	29 (18.5)	3 (15.8)
	Annual joint bleed Rate	Mean (SD)	0.39 (1.12)	0.28 (0.78)
		Median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
Left elbow	Joint bleed prevalence	n (%)	35 (22.3)	2 (10.5)
	Annual joint bleed Rate	Mean (SD)	0.81 (2.38)	0.17 (0.53)
		Median (IQR)	0.0 (0.0;0.0)	0.0 (0.0;0.0)

Joint bleed prevalence (%): Numerator= number of patients who had bleeds, Denominator= total cohort number. *Patients may have reported bleeding at more than one joint over the 12 month study period

3.5.2 Haemophilia joint health scores

HJHS are presented in Table 2 as all recorded joints combined (total), and individual joint score by the site (ankle, knee, elbow), and side (left/right). In adults total median (IQR) HJHS were higher in haemophilia A with a total HJHS of 18.0, (6.0; 31.0) when compared to 11.0 (5.0; 24.0) for haemophilia B. At an individual joint level, both mean and median ankle HJHS (3.8, 4.0) were higher than for the knee (2.9, 1.0) and elbow (3.3, 1.0). Likewise, IQR was higher in the ankles (0; 8.0).

Table 2: Total and individual HJHS

Joint		Haemophilia A (n=157)	Haemophilia B (n=19)
All Joints	**Mean (SD)**	21.2 (16.8)	15.4 (15.1)
	Median (IQR	18.0 (6.0;31.0)	11.0 (5.0;24.0)
Right Ankle	**Mean (SD)**	4.6 (4.2)	3.6 (4.1)
	Median (IQR	4.0 (0.0;8.0)	2.0 (0.0;7.0)
Left ankle	**Mean (SD)**	4.6 (4.3)	4.8 (4.1)
	Median (IQR)	4.0 (0.0;8.0)	4.0 (1.0;8.0)
Right knee	**Mean (SD)**	2.7 (3.9)	2.5 (4.6)
	Median (IQR)	1.0 (0.0;4.0)	0.0 (0.0;1.0)
Left knee	**Mean (SD)**	2.9 (4.1)	1.3 (2.2)
	Median (IQR)	1.00 (0.0;5.0)	0.0 (0.0-2.0)
Right elbow	**Mean (SD)**	3.3 (4.1)	1.3 (2.6)
	Median (IQR)	1.0 (0.0;7.0)	0.0 (0.0;1.0)
Left elbow	**Mean (SD)**	3.2 (4.2)	2.1 (4.0)
	Median (IQR)	1.0 (0.0;6.0)	0.0 (0.0;1.0)

3.6 Discussion

This study aimed to examine the current joint bleed prevalence and incidence of haemarthrosis, with a particular focus on the ankle in adults with severe haemophilia A and B, without a current inhibitor. The impact of haemarthrosis on ankle health and its relationship to other commonly affected joints were collated to provide insight into the effect of haemarthrosis on joint health.

Data presented in this chapter identifies that despite prophylaxis, the prevalence of haemarthrosis in those with severe haemophilia without a current inhibitor and compliant with treatment has seen only minor reductions in the incidence of haemarthrosis despite advances in treatment [4]. Whilst the incidence of haemarthrosis is evenly distrusted amongst the most commonly affected joints of the upper and lower limbs, those CCC and HC reporting concurrent HJHS indicate that the ankle joint is disproportionately affected by haemarthropathy.

Mean and median AJBR totals (Table 1) were higher in people with haemophilia A than haemophilia B. Total joint bleed prevalence of (Table 1) 60% and 41% respectively indicate that those patients deemed the most compliant with recording treatment experienced a minimum of one haemarthrosis over the 12 month study period. Study results are consistent with published data that a higher prevalence of joint bleeding occurs in haemophilia A [1, 4]. Those with haemophilia B have a less severe bleeding phenotype, lower bleed frequency and better long term outcomes [234, 235]. Ultimately haemophilia treatment aims to prevent all incidences of bleeding, but low rates of haemarthrosis may be unavoidable with current haemophilia treatments [236].

Based on the haemarthrosis prevalence in 2018 a single incidence of joint bleeding may have detrimental effects on joint cartilage, leading to the deterioration of joint health [237-239]. Our study only reports data from a single year and cannot describe previous haemarthrosis data in this cohort. Therefore we are unable to report the previous bleed profiles of those included in this study or provide a direct causal effect of a single

haemarthrosis. Relatively small volumes of blood have been shown to cause changes in cartilage matrix properties and in vitro cartilage exposures of blood products as low as 10% cause irreversible damage at two days after exposure [62]. Furthermore, where joint health continues to deteriorate the concept of low-level bleeding, micro-bleeding and subclinical bleeding have been proposed as a mechanism by which joint health continues to decline [46, 55]. Low-level incidence of clinical undetectable joint haemarthrosis may be sufficient to initiate or maintain primary effects of blood exposure by haemosiderin burden and pro-inflammatory markers causing secondary effects to synovitis and pro-inflammatory cytokines and proteases. There is yet to be any definitive study that supports clinical non-detectable haemarthrosis as a significant contributor to the decline in joint health [52, 240]. The results of this study, whilst descriptive support the notion that whilst bleed rates are low in established haemarthropathy and where treatment compliance is high bleeding still occurs. In joints that are already burdened with arthropathic changes, this single joint bleed event may be sufficient enough to overload the joint with inflammatory markers, exceed the capacity of synovial removal of haemosiderin and initiate further joint decline.

AJBR incidence presented in Table 2 are slightly lower than that of the THUNDER study that, produced three years earlier from the same NHD database [4]. Scott *et al.* (2019) identified that patients with severe haemophilia receiving prophylaxis and compliant with Haemtrack (n=607) reported a median AJBR of 2.0 (0.0-6.0) of adults aged 19 and above. The median AJBR is similar in our study cohort of 1.0 (0.0; 4.4) hence in the three years between the THUNDER study there has only been a slight decrease in AJBR. In this 2018 NHD cohort around a quarter of those sampled used EHL products with 96% of those sampled compliant with prophylaxis which may provide insight to this chapter finds as EHL were not commonly prescribed at the time of Scott *et al*. (2019) THUNDER study. In addition, the THUNDER study did not include those with haemophilia B, which as alluded to, display less severe AJBR, ABR and haemarthropathy. Lower rates of joint deterioration and severity in the haemophilia B population may explain the slight

decrease in our study data [235]. Direct comparisons between disease types are limited and therefore requires further exploration to determine whether lower bleed rates and better joint health in the haemophilia B cohort have external validity. Around 30% of the participants sampled in this study used EHL treatment to manage their haemophilia. The data collected in our study suggests EHL products make only slight differences to the UK bleed rates. Studies of EHL factor VIII and IX levels report a 1.5 to 1.6 fold longer drug half-life than standard products [241, 242]. In addition, ABR in patents on EHL treatment are reported to decline by 20% to 50% with higher trough levels than SHL products, but the data collected in this study does not support findings as the overall effect on ABR were only slightly reduced in our study with 30% of participants on EHL products [242]. A definitive study is yet to be undertaken to obtain the true efficacy and effect of EHL products on ABR, AJBR and joint disease [241]. Longitudinal follow-up of Dutch adults with severe haemophilia A and B (n=62) treated by prophylaxis reported that over a 5-10 year period that median AJBR (IQR) of 0.0 (0.0-2.0). However, despite the low incidence of haemarthrosis joint health continued to decline [243]. HJHS scores increased by 4 points over the study period in 37.1% of patients, with the ankle joint the most affected and accounting for 30.6% of the decline in overall joint health [243]. The low AJBR and increased HJHS support the findings described in this chapter which indicate that even with very low AJBR joint health declines despite controlled prophylaxis treatment regimens.

Mean HJHS at the ankle joint were similar to the elbows followed by the knee indicating the clinical impaction of haemarthrosis is evenly distributed amongst the most commonly reported and affected joints. Interestingly the median scores at both the knee and elbow (1.0) were lower than that of the ankle (4.0 (0.0; 8.0)) suggesting that there is worsening ankle joint health when compared to other joints. It remains unclear as to why the ankle joint is disproportionally affected by haemarthropathy. Structural and mechanical change at the ankle contributes to abnormal loading forces during the stance phase of gait. In combination with soft tissue changes, the ability to store and release energy from the

gastro/soleus complex is compromised, therefore structural and functional changes compromise ankle integrity [8, 166]. Similarly, where changes occur to the bone surfaces of the talus and tibia, contact forces are greatly increased further adding to the detriment of the joint [18]. While ABR and AJBR continue to decline higher levels of haemarthropathy are still reported at the ankle joint. Increased frequency of ankle haemarthropathy may be attributed to the complexities of the ankle joint complex and biomechanical changes, although functional biomechanical changes may not present until adulthood [8, 86, 229]. Moderate correlation of the HJHS with radiological scores at the ankle joint warrants exploration of other markers that determine joint changes. Physical assessment by HJHS lacks the sensitivity to identify active non-detectable haemarthrosis at the ankle. Therefore additional measurements such as diagnostic and point of care musculoskeletal ultrasound may be required to ascertain true ankle joint status [209].

Haemarthrosis prevalence and joint health have been reported in children as per the method described in section 3.3 [244]. A total of 97 children with haemophilia A (n=80) and with haemophilia B (17) with a median (IQR) age of 10 (7; 13) and 12 (7; 14) respectively were included with joint bleed prevalence and HJHS. Prevalence's in the paediatric cohort were lower than adult data with 32.5% of haemophilia A and 47% of haemophilia B children recording at least one haemarthrosis over the 12 month study period. Clinically detectable changes in joint structure and function were not detected by the HJHS. Mean and median scores were 0.00 (0.00-0.00), therefore data suggest that clinical signs of haemarthropathy are yet to occur in younger children, or is not detectable using the HJHS in those compliant with treatment. Our study indicates the HJHS is not sensitive to changes in children, or physical joint changes in children have not occurred. This study supports the notion that HJHS measures the cumulative effect of haemarthropathy, usually not clinically detectable until later years [240].

A limitation of this study is the relatively small number of patients registered on the UK database who had full Haemtrack and concurrent itemised HJHS recorded at the time of

data collection. The NHD does not report bleed level data on patients who do not report treatment using Haemtrack, thus limiting the sample size. Those patients included in the analysis were self-reporting and therefore more likely to be compliant with treatment. Bias may be introduced by the inability to include those not reporting treatment. Likewise where HJHS were not reported electronically by CCC and HC, or itemised by total and individual joint scores and therefore did not meet the NHD criteria for analysis. The small sample size in our study highlights the need for the collation of HJHS by electronic reporting across all UK centres, which would increase the sample size in future studies.

The sample of haemophilia B patients included in this analysis was small and therefore clinical interpretation of joint bleed prevalence and HJHS between haemophilia A and B should be interpreted with caution. Haemophilia A is associated with higher rates of bleeding and studies of haemophilia B report lower bleed rates, fewer complications and delayed progression and severity of haemarthropathy [234, 235]. Research with larger samples of haemophilia B patients is required to understand whether the lower bleed rates and lower levels of haemarthropathy reported in this study are generalisable to the haemophilia B population. A further limitation is the variation of between-centre scoring of the HJHS data. Different haemophilia centres may be subject to inter-centre scoring variability, although regular workshops are conducted in the UK to decrease inter-centre variability in HJHS scoring [245]. Furthermore, we are unable to confirm the influence of other factors such as the presence of co-morbid musculoskeletal conditions on HJHS data. UKHCDO NHD data was requested from those with a moderate disease type but there was insufficient data to include in the analysis. Future comparison by disease severity (severe and moderate) may provide further insight to those most at risk of haemarthropathy.

3.7 Conclusion

In the UK, joint bleed prevalence of incidence haemarthrosis has changed little in the three years since the publication of the THUNDER study. In this 2018 cohort of severe haemophilia patients without a current inhibitor, only 30% of adults remained haemarthrosis free. Ankle joint haemarthrosis rates were comparable to that of the elbow in haemophilia A, and the elbow was the most frequent joint affected in adults with haemophilia B. However, higher HJHS were reported at the ankle joint compared to the knee and elbow, confirming that the ankle joint is the most affected by haemarthropathy. Understanding the impact of ankle haemarthrosis and subsequent haemarthropathy may provide insight into the disparity between the ankle and other commonly affected joints of the musculoskeletal system. Other contributing factors such as pain, treatment and access to clinical services may provide future direction and research priorities. Future clinical studies would benefit from understanding the bleeding profiles of those who do not meet compliance or criteria for Haemtrack to obtain the true prevalence of haemarthrosis. Current ankle joint bleed prevalence and associated impact on the musculoskeletal system justifies the investigation of the impact on QoL and foot and ankle specific outcomes in patients with ankle haemarthropathy across haemophilia types, severity and treatment regimes.

Chapter 4 - The impact of blood induced ankle arthritis in patients with moderate and severe haemophilia A and B: The HAPII study

This chapter investigates the impact of haemarthrosis and haemarthropathy of the ankle. A cross-sectional questionnaire was used to establish the impact of blood induced ankle arthritis in people with moderate and severe haemophilia A and B. Haemophilia Consultants across the UK were also surveyed to provide a snapshot of services available to those with haemophilia and haemarthrosis induced ankle arthritis.

A full review of literature has been undertaken in chapter two, therefore a brief introduction will provide detail on the impact of blood induced ankle arthritis in moderate and severe haemophilia A and B.

4.1 Introduction

Despite prophylaxis, adults with severe non-inhibitor haemophilia A and B still experience haemarthrosis and develop haemarthropathy of the upper and lower limbs. The data presented in Chapter Three identified that in patients with ≥75% adherence to prophylaxis, most reported a minimum of one episode of haemarthrosis over 12 months and a decline in joint health status. A single episode of haemarthrosis may be unavoidable due to the balance of clinical effectiveness, risks and cost of treatment, with treatment regimens aimed at trough levels similar to moderate haemophilia (0.01 to 0.05 IU/mL) that halt spontaneous haemarthrosis and minimise traumatic bleeding [4, 29].

European and UK studies report sub-optimal treatment regimens despite the availability of clotting factor concentrates (CFC) in western medicine [4]. Data from individuals with moderate haemophilia report a higher incidence of bleeding despite prophylaxis with an annual bleed rate (ABR) ranging from 2.0 to 8.0 across Europe. In the UK, median (IQR) ABR and annual joint bleed rate (AJBR) ranging from 3.0 (1.0 to 7.0) and 2.0 (2.0 to

15.3), respectively, in moderate haemophilia (n=154). In severe haemophilia, AJBR and ABR are similar indicating that in the sample of moderate haemophilia patients treated with prophylaxis 81% had a bleed and 72% had a minimum of one episode of haemarthrosis [4]. This suggests that those with moderate haemophilia with a bleeding phenotype are at risk of the same levels of joint damage seen in severe disease, yet moderate factor levels have been a treatment target (>0.01 to <0.05 IU/mL) of severe haemophilia for a number of years [221, 246]. AJBR of 3.5 (0.0 to 12.8) in patients treated on-demand with severe haemophilia is without surprise higher than for those on prophylaxis. Likewise in moderate on-demand treatment cases, AJBR is higher at 5.0 (2.0 to 15.3), exposing joints to worsening musculoskeletal health [4]. AJBR is a concern across haemophilia severities and treatment regimens as a treatment target for prophylaxis. Specifically, more than two bleeds within six months lead to the development of target joints that are more prone to bleed and represents an indication of under treatment [44]. It is clear that despite the availability of CFC, haemarthrosis cannot be avoided. Measurement of ABR and AJBR outcomes by haemophilia type (A, B), severity (severe, moderate) and treatment regime (prophylaxis/ on-demand) is difficult, due to the reliance of patients reporting treatment and incidence of bleeding. The UKHCDO NHD only report data on treatment ≥75% delivered vs recorded treatments over 45 weeks, a minimum requirement for reporting “good data” [231]. Little is reported therefore on patients who do not meet this ≥75% threshold and so a significant proportion of the haemophilia population that may not be fully compliant with treatment and/or report haemarthrosis are not included in analysis. This therefore likely underestimates the true clinical impact on musculoskeletal health in the UK [231] as joint damage is likely to be worse in more poorly complaint patients than in the cases included in NHD-based reports.

The physical and mental burden of haemarthropathy is great when compared to the general population. Change to joint status is a significant contributor to the decline in HRQoL as well as pain and functional impairment [10, 11]. The severity of haemophilia

is associated with worse HRQoL, with people with severe haemophilia the worst affected when compared to moderate and mild disease types [247]. A Dutch study of haemophilia and social participation reported that adults with severe haemophilia (n=144) born before the introduction of prophylaxis (30 to 65 years old) reported lower levels on the SF-36 HRQoL compared to the general population in all domains except mental health. Mean (SD) scores (out of 100) physical function (45.9 (28.5), 84.0 (19.6)), role physical (67.4 (42.9), 81.6 (33.2)) and role emotional (67.4 (42.9), 81.6 (33.2)) respectively, were particularly reduced compared to the general population. Those with severe haemophilia born after the introduction of prophylaxis (15 to 30 years) reported higher scores than older adults, but still lower than the general population, specifically in physical function (82.2 (21.4) 93.1 (11.8)), role function (73.0 (38.0), 86.4 (27.6)) and general health 69.9 (22.2), 78.4 (17.3)) respectively. The sample of respondents with moderate and mild levels of haemophilia (n=244) reported no differences in HRQoL compared to the general population [247]. Low QoL appears to be associated with delayed prophylaxis and associated haemarthropathy. Whilst overall QoL is informative, the inclusion of a joint health measure such as the HJHS or factor treatment levels may provide further insight to physical and pharmacological impact on HRQoL [247]. In a US study (n=381) of haemophilia care, Kempton *et al.* (2017) explored the contribution of haemarthrosis, joint pain and functional impairment on QoL in severe, moderate and mild haemophilia [10]. Median (IQR) SF-36 scores were lower for the four physical domains of physical function (44.4 (29.7 to 52.8)), physical health (39.2 (29.5 to 49.4)), and body pain (41.8 (37.2 to 51.1)) thus indicating poor HRQoL. The absence of a control group make comparison to the general US population difficult, but scores were similar to Plug *et al.* (2008) and support the detrimental effect of haemarthrosis, haemarthropathy, functional impairment and pain on the HRQoL across the range of haemophilia severities [10, 247].

Over 50% of people with haemophilia report acute and chronic joint pain related to disability and impairment, a major factor in the determination of HRQoL [248, 249]. The significance of pain to HRQoL has been examined by Wallny *et al.* (2001) who

investigated the contribution of multi-joint severe haemarthropathy using a bespoke pain questionnaire (n=71) [250]. The impact of HRQoL was significant, with difficulties performing activities of daily living (ADL). Though mental health has been unaffected in Dutch haemophilia cohorts Wallney *et al.* (2001) indicate that low mood contributed to moderate levels of QoL [247]. Although little detail was provided on how QoL and ADLs were measured the largest contributing factor was pain. The ankle joint (45.1%, n=32) was the largest contributor to pain followed by the knee (39.4%, n=28), back (14.1% n=10) and elbow (7.0%, n=5). Whist the authors provide no details on how haemarthropathy was measured, the study reported 76.1% requiring analgesia daily to alleviate pain [250].

The ankle is a problematic joint in the treatment and management of pain and haemarthropathy in haemophilia [9, 19, 250]. Changes in structure, function and pain suggest the ankle may disproportionally affect QoL, pain and disability compared to other commonly affected joints, with the ankle joint often cited as the worst affected in terms of function, higher levels of joint pain and the most frequent site of haemarthrosis [9, 19, 250]. Whilst prophylaxis reduces AJBR, ankle joint status continues to deteriorate even where bleeding is not clinically apparent [46, 55]. In UK adults, the true impact of ankle haemarthrosis and haemarthropathy on haemophilia type, severity and treatment regimen is yet to be established.

4.2 Study aims

The primary aim of this study was to establish the impact of haemarthrosis and associated haemarthropathy of the ankle joint in patients with moderate and severe haemophilia A and B with and without a current inhibitor. Secondary aims were to understand the effect of patient-reported pain, anatomical sites of haemarthropathy, treatment regime, and patient-perceived access to clinical services. Finally, a consultant survey provided a snapshot evaluation of clinical services relevant to the management of haemarthropathy with a focus on the availability of foot and ankle services.

4.3 Methods

Ethical approval was obtained on 24th January 2017 (IRAS: 206141, R&D: PD16/227). Recruitment commenced on 13th April 2017 and ended on 31st August 2019. Recruitment was across multiple sites across England, Scotland and Wales, with support from the NIHR clinical research network (non-malignant haematology). A principal investigator (PI) identified at each site oversaw implementation, approach, consent, and data collection. Anonymised questionnaire data was returned to the primary site (Leeds) for data entry and analysis.

4.3.1 Patient impact questionnaire (study one)

A cross-sectional multi-centre survey was conducted at 18 national sites, consisting of 13 haemophilia comprehensive care centres (CCC) and five associated haemophilia treatment centres (HC) in England, Scotland and Wales. The survey aimed to explore the association between ankle joint haemarthrosis and subsequent ankle haemarthropathy on patient-reported QoL, ankle/foot pain and disability. The questionnaire was divided into section A for patient completion and section B, clinical details completed by the site PI or research staff member. Details related to weight, height, surgical history, and ankle HJHS were collected (Appendix 1).

The questionnaire was administered by the participating centre's doctor, nurse or allied health professional (AHP). Patients were provided with a patient information sheet (PIS) and given a minimum of 15 minutes to consider participation. Potential patients were encouraged to ask questions about the study and advised to take the PIS home if they required a longer period of consideration. Once participation was agreed, written, informed consent was obtained and the questionnaire completed. Patients were provided with a copy of the PIS and consent form. A copy of the consent form and PIS were also either uploaded to or filed in the patient's medical record.

4.3.2 Inclusion/ exclusion criteria

Patients recruited to this study were required to have a consultant diagnosis of ankle haemarthropathy with haemophilia A (factor VIII) or B (factor IX), with moderate (≥0.01 IU/mL) or severe (<0.01 IU/mL) levels of factor deficiency as defined by the International Society on Thrombosis and Haemostasis (ISTH) [221]. The eligibility criteria are summarised in Table 3. Participants were male-only due to the X-linked recessive inheritance nature of the disease. Similarly, participants were not aged-matched to other disease types such as ankle OA owing to the early initiation of ankle joint disease. OA cohorts typically 20 to 30 years older with the mechanism of injury is traumatic or inflammatory in nature [251].

Table 3: Inclusion/ exclusion criteria

Inclusion criteria	Exclusion criteria
• Haemophilia A or B, moderate or severe defined as a plasma factor level of less than five percent (<5 IU dL-1) • A consultant diagnosis of haemarthrosis induced ankle haemarthropathy • Aged 16 or over • Patients who can give informed written consent • Males	• Other bleeding disorders such as Von Willebrand disease • Mild haemophilia A and B • Significant comorbidities such as diabetes and inflammatory arthritis that are associated with lower limb vascular and neurological defect leading to altered foot and ankle biomechanics and abnormal sensation/ pain perception

4.3.2.1 Patients use of clinical services

To obtain insight into the current care provision of those with ankle haemarthropathy, patients were asked to provide detail on certain aspects of their clinical care related to access to the following clinical specialists; physiotherapist, podiatrist/chiropodist for musculoskeletal assessment and foot orthoses provision. Patients were asked if they had access to a podiatrist/chiropodist for nail cutting and callus removal (routine podiatry

treatment). Details of hospital or adapted shoes were recorded as were insole provision and type (shop brought, NHS supplied, private podiatrist supplied).

4.3.2.2 Clinician reported participant details

Details of patient demographics (height, weight, and baseline factor levels), and treatment (prophylaxis years, treatment trough level, product, product change in the past 12 months) were recorded. HJHS or ankles were reported as a single joint score per side (left/right). Haemtrack participation status, ankle joint bleeds reported over the past 12 months and the imaging modality used to confirm haemarthropathy (US, MRI, X-ray) were recorded. Finally, the history of ankle surgery by the site (left/right) and procedure were collated.

4.3.3 Impact patient questionnaire

4.3.3.1 Haemophilia disease and management

Demographic data were collected for each patient consisting of haemophilia type (A or B), severity (moderate or severe), treatment regime (prophylaxis or on-demand) frequency of infusion, dose (IU/kg) and inhibitor status. Patients were also asked to provide information on amounts of extra replacement CFC used per day when a bleed occurred and on average how many extra days replacement therapy was taken following a participant-perceived mild bleed or a severe bleed. A list of potential target joints, defined in this study as those affected by haemarthropathy, were provided based on affected joints by the site (ankle, knee, hip, wrist, elbow, shoulder) and side (left and right). Patients were also asked to provide a self-reported number of ankle bleeds (left and right) over the last 12 months and whether any ankle surgery had taken place (left or right).

4.3.3.2 Patient-reported outcome measures (PROMs)

To explore the impact of ankle haemarthropathy on health-related quality of life (HRQoL), a disease-specific HAEMO-QoL-A and the foot-and-ankle-specific measure the Manchester Oxford Foot and Ankle Questionnaire (MOXFQ) were collected. No other HRQoL or PROM were used based on the burden of research questionnaire data collection.

4.3.3.3 Haemophilia quality of life in Adults (HAEM-QoL-A)

This is a validated haemophilia specific HRQoL tool, consisting of 41 questions scored in six subscales of functional activity, role function, worry, consequences of bleeding, emotional impact, and treatment concerns [201, 252]. For each question, a six-point Likert scale is used, ranging from 0 (None of the time) to 5 (All of the time) yielding a domain score for each of the six subscales with a higher score indicating better health. Raw scores are combined to produce a total score (0 to 100), with 0 indicating worse possible health and 100 best possible health [200]. Whist limitations of the HAEMO-QoL-A have been identified in cross-cultural validity, compared to generic QoL measures such as the SF-36, the HAEMO-QoL-A displays moderate to strong correlation in pain, social function, and role limitations [200, 202, 203]. Despite these limitations, the HAEMO-QoL-A is the most widely used and clinically validated measure of HRQoL in haemophilia to date [253].

4.3.3.4 Manchester Oxford Foot Questionnaire (foot and ankle) (MOXFQ)

The MOXFQ is a PROM used to evaluate foot and ankle pain, consisting of three domains of walking/standing, pain and social interactions. A higher score (0 to 100) indicate worse severity [213, 217-219]. The MOXFQ, when compared to other foot and ankle PROMs, performed the best in psychometric properties, internal consistency, reliability, measurement error, structural, convergent, discriminant, discriminative validity and responsiveness [220]. The MOXFQ is yet to be utilised in haemophilia foot and ankle research, but in a condition characterised primarily by the talocrural joint involvement, the use of a MOXFQ outcome measure is appropriate.

4.3.3.5 Pain measures

Patients were asked to provide detail on how they would describe a joint bleed, whether they took any medication for pain and what medications they currently took for joint pain. Details of patient-reported pain were captured using an 11 point (0 to 10) numerical pain rating scale (NPRS) and a Likert scale (discussed in section 4.3.3.3) to identify the change in pain related to episodes of haemarthrosis and use of Factor treatment following an acute, mild and severe haemarthrosis.

4.3.3.5.1 NPRS development

All pain measures were developed using the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines for the management of chronic pain and tested in a cohort of potential patients (n=12) in the initial questionnaire design and final terminology used [254].

In this pilot pain questionnaire () participants were asked to rank three questions for each outcome based on the best to worse relevance for “pain over the past six months”, “thinking about ankles after an acute bleed” and “factor use after an episode of bleeding”. The wording of each question was then ranked for relevance from 1= best and 3= worst. The following responses were ranked as “best” by patients and most relevant in capturing the effect of any ankle pain;

Pain in your ankle over the last six months

“How painful has your ankle been over the past six months?” (n=7, 58.3%)

Please think about your ankles after an acute bleed

How much pain do you have in your ankle straight after a bleed? (n=9, 75%)

Think about factor use when you have had a bleed?

You have had a bleed and treated it with factor. How much improvement do you have in pain after your usual extra treatment period? (n=8, 66.6%)

The patient selected questions were then included in the pain section of the HAPII patient questionnaire and adapted to measure pain following an acute, mild and severe ankle bleed (Appendix 2).

4.3.3.5.2 Final pain measures

Patients were asked to provide a score for ankle pain over the past six months, and pain immediately following a bleed. Zero indicates no pain and 10 pain is as bad as you can imagine. Picture mapping based on the Garrow *et al*. (2000) foot manikin was used to identify common sites associated with ankle haemarthropathy [255]. Picture mapping was provided as part of the questionnaire and patients were asked whether they had experienced foot or ankle pain lasting at least one day during the past month. If the participant shaded multiple diagrams across the picture mapping they were then required to add an arrow indicating the most painful site.

4.3.4 Consultant online survey (study two)

A simultaneous online haemophilia consultant survey (Online surveys, Bristol, UK, Jisc 2021) was undertaken and distributed to all UKHCDO member haemophilia consultants across the UK (Appendix 3). A description of the study was provided with the HRA registration number and study team contact details in an approach email. Consent was provided by participation and submission of the online survey for analysis.

4.3.4.1 Consultant survey

Consultant haematologists were assessed to provide details of the services provided at their haemophilia CCC or HC related to the management of haemophilia, MSK disease and UKHCDO care standards [12]. The following questions; access to core services of foot and ankle orthopaedics, rheumatology, psychology, radioactive synovectomy, point of care ultrasound (POCUS) and physiotherapy services. In addition, consultants were asked to provide details specific to the management of the foot and ankle by orthotics services, and podiatry for MSK assessment and provision of foot orthoses and access

to podiatry for routine foot care for nail and skin (callus, corns) care. For each question, the consultant was required to indicate whether access was available within their haemophilia centre, externally via a general practitioner (GP) or did not have access.

4.4 Statistical methods

All data were entered into Statistical Package for the Social Sciences (SPSS) version 26 (Armonk, NY: IBM Corp). A recruitment target of 245 was set to allow the mean HAEM-QoL-A to be estimated to be within ±2.5 units of the measurement scale, assuming a between the patient standard deviation of 16.96 [200]. To predict participant disease states, HRQoL and PROMs data were entered as outcomes into a linear regression analysis, where the effect of participant haemophilia type (A or B), severity and treatment regime (prophylaxis or on-demand) were added separately as indicators of direct relationship. Clinical characteristics (severity, treatment etc.) were then added as additional indicators. Complete cases were analysed under the assumption that any missing data were missing completely at random. A 2-sided 5% significance level was used throughout. Test of normality was undertaken to assess the skewness of data and the appropriateness of the statistical methods used. Finally, regression analysis was undertaken to determine whether there were direct relationships between clinical characteristics and decline in HRQoL and PROM. Variable including numerical pain rating scales, inhibitor status HJHS and treatment amount (IU/kg) were entered using stepwise regression analysis to explore whether the clinical variables had a direct relationship to decline in HRQoL and PROM. Parametric data are presented as mean and standard deviation (SD); non-parametric data as the median and interquartile range (IQR). Frequency data is presented as total numbers and percentages.

4.5 Results

4.5.1 Descriptive statistics

At the close of recruitment, 250 response sets had been received. Data from seven patients were excluded from the analysis due to the incompleteness of the primary outcome measures (HAEMO-QoL-A and MOXFQ), leaving 243 for primary and secondary analysis.

4.5.1.1 Haemophilia disease and management

Overall, 214 (88.1%) patients had severe and 29 (11.9%) had moderate haemophilia. Participant characteristics by haemophilia type and severity are presented in Table 4. Those with severe haemophilia A made up the largest proportion of patients. Age, height and weight were similar across haemophilia type and severity. BMI was similar across haemophilia types, with the majority of patients classed as over-weight.

Table 4: Study participant characteristics

Severity and treatment		Haemophilia A	Haemophilia B
Severe Mean (SD)	Number	184/ 75.7%	30/ 12.3%
	Mean (SD) age	42.4 (13.1)	47.3 (11.5)
	Prophylaxis	164 / 67.5%	27/ 11.1%
	On-demand	20/ 8.2%	3/ 1.2%
	Current inhibitor	16/ 6.6%	1/ 0.4%
	Height (cm)	176.9 (7.4)	177.6 (7.3)
	Weight (Kg)	84.1 (18.3)	89.4 (19.9)
	BMI (Kg/m^2)	26.7 (5.3)	27.8 (7.1)
Moderate	Number	25/ 10.3%	4/ 1.7%
	Age	48.9 (15.9)	46.6 (18.1)
	Prophylaxis	11/ 4.5%	3/ 1.2%
	On-demand	14/ 5.8%	1/ 0.4%
	Current inhibitor	1/ 0.4%	0
	Height (cm)	177.2 (7.9)	180.6 (9.6)
	Weight (Kg)	85.0 (16.2)	98.4 (18.9)
	BMI (Kg/m^2)	26.8 (4.4)	30.1 (4.5)

4.5.1.1.1 Prophylaxis regimes

Details of prophylaxis, treatment frequency and those who treat on-demand are listed in Table 5. Overall, 242 out of 243 patients provided detail. The most common treatment regimens were alternate day prophylaxis, followed by daily treatment across haemophilia types.

Table 5: Prophylaxis treatment characteristics			
Severity and treatment frequency		**Haemophilia A**	**Haemophilia B**
Severe (n=213)	**Daily**	24 (9.9%)	0
	Alternative days	93 (38.4%)	4 (1.7%)
	Five times per week	2 (0.8%)	0
	Three times per week	6 (2.5%)	0
	Twice per week	26 (10.7%)	5 (2.1%)
	Once per week	4 (1.7%)	18 (7.4%)
	BsMAb	9 (3.7%)	n/a
	On-demand	20 (8.3%)	3 (1.2%)
Moderate (n=29)	**Daily**	0	1 (0.4%)
	Alternative day	7 (2.9%)	1 (0.4%)
	Five times per week	0	0
	Three times per week	0	1 (0.4%)
	Twice per week	2 (0.8%)	0
	Once per week	2 (0.8%)	0
	On-demand	14 (5.8%)	1 (0.4%)

4.5.1.1.2 Treatment products

Patients receiving standard half-life (SHL) CFC treatment were exclusive to haemophilia A, with 107 (45.3%) patients receiving this. Extended half-life (EHL) products were used by 88 (37.38%) and 32 (13.55%) patients with haemophilia A and B respectively. Nine (3.8%) patients used a bispecific monoclonal antibody (BsMAb**),** which at the time of this study, were used exclusively in the management of haemophilia A with a current inhibitor.

4.5.1.1.3 Prophylactic treatment of haemophilia

Complete and detailed treatment data was only available for 213 out of 243 patients. CFC treatment characteristics are presented in Table 6. Median (IQR) treatment dose by IU/kg was similar across haemophilia types but in both haemophilia, A and B higher doses were reported in those with moderate disease types.

Table 6: Clotting factor concentrate treatment characteristics

Type	**Haemophilia A**				**Haemophilia B**			
Severity	**Severe**		**Moderate**		**Severe**		**Moderate**	
Treatment (n=213)	**Prop (n=112)**	**OD (n=16)**	**Prop (n=11)**	**OD (n=3)**	**Prop (n=27)**	**OD (n=3)**	**Prop (n=3)**	**OD (n=0)**
IU/kg, Median (IQR)	26.9 (19.9; 32.1)	25.5 (24.2; 34.0)	28.2 (23.5; 30.4)	26.3 (-)	29.6 (20.2; 38.6)	30.5 (-)	28.4 (-)	-

*Prop= prophylaxis, OD= on demand *= ≤3*

4.5.1.1.4 Treatment of haemarthrosis

The characteristics of haemarthrosis treatment are presented in Table 7. Median (IQR) treatment characteristics are presented and are representative of participant treatment habits for the management of haemarthrosis. The patient's IU/kg of CFC treatment increased by 5.2 IU/kg and 5.4 IU/kg in severe haemophilia A prophylaxis and on-demand treatment respectively. The number of extra treatment days was similar across groups for mild (1 to 2) and severe (3 to 4) bleeds. Participants' ankle AJBR were generally higher in the moderate haemophilia groups, but again similar across treatment types.

Table 7: Characteristics of haemarthrosis treatment

Type	**Haemophilia A**				**Haemophilia B**			
Severity	**Severe**		**Moderate**		**Severe**		**Moderate**	
Treatment Median (IQR) (n=213)	**Prop (n=112)**	**OD (n=16)**	**Prop (n=11)**	**OD (n=3)**	**Prop (n=27)**	**OD (n=3)**	**Prop (n=3)**	**OD (n=0)**
Bleed IU/kg	32.1 (25.0; 46.7)	30.9 (24.2; 47.1)	29.9 (26.7; 31.3)	21.3 (-)	34.3 (21.3; 44.1)	40.7 (-)	28.4 (-)	-
Treatment days - mild bleed	1 (1; 2)	1 (1; 2)	2 (2; 3)	2 (-)	1.0 (1; 2)	2.0 (-)	2.0 (-)	-
Treatment days – severe bleed	3 (2; 4)	3 (2; 4)	4 (4; 7)	3 (-)	3.0 (3; 5)	4.5 (-)	6.0 (-)	-
Right ankle bleeds last 12 months	1 (0; 3)	0 (0; 2)	1 (0; 1)	0 (-)	0 (0; 1)	0.5 (0.7)	1 (-)	-
Left ankle bleed last 12 months	0 (0; 2)	0 (0; 2)	1 (0; 3)	4.0 (-)	1 (0; 2)	1.5 (-)	3.0 (-)	-

*Prop= prophylaxis, OD= on demand *= ≤3 treatment doses are presented as medians to represent clinical treatment doses, ie drug is supplied to the patient in 500ui vials.*

4.5.1.2 Pain

4.5.1.2.1 Ankle pain characteristics

Ankle pain characteristics are presented in Table 8 as mean (SD) with data available for 220 out of 243 patients. Ankle pain severity experienced over the last six months was consistent across haemophilia type and severity regardless of treatment type. Pain experienced following an acute bleed was also consistent with a 1 to 2 point increase in pain following an acute episode of bleeding. Patients reporting use of CFC treatment following a severe or mild bleed report “much improved” pain for both incidence of mild and severe haemarthrosis.

Table 8: Pain characteristics

Type	Haemophilia A				Haemophilia B			
Severity	Severe		Moderate		Severe		Moderate	
Pain scales Mean (SD)	Prop (n=150)	OD (n=18)	Prop (n=11)	OD (n=10)	Prop (n=26)	*OD (n=3)	*Prop (n=3)	*OD (n=1)
Ankle pain in the past six month (NPRS 0-10)	5.1 (2.6)	5.5 (3.0)	5.8 (2.6)	4.8 (2.7)	5.3 (2.3)	5.0 (0.0)*	6.0 (3.6)	5.2 (0.0)
Ankle pain after an acute bleed (NPRS 0-10)	7.1 (2.0)	6.9 (2.8)	6.9 (2.2)	6.6 (1.4)	7.4 (1.9)	9.5 (0.7)	7.0 (3.0)	9.5 (0.0)
Ankle pain response to factor – Mild bleed (n=225)	1.2 (0.8)	1.3 (0.9)	1.0 (0.5)	1.3 (0.7)	1.1 (1.1)	1.0 (0.0)	0.7 (0.6)	-
Ankle pain response to factor – Severe bleed (n=223)	1.5 (0.8)	1.5 (.7)	1.3 (0.7)	1.5 (0.5)	1.5 (1.3)	2.0 (0)	1.0 (0.6)	-

*Prop= prophylaxis, OD= on demand *= ≤3*

4.5.1.2.2 Pain medication

Complete data on pain medication was available for 233 out of 243 patients. Overall, 131 (56.2%) patients did not take regular pain medication, and 102 (43.7%) patients used regular pain medication. The most commonly used analgesics were paracetamol and COX2 inhibitors (see Table 9). The most common combination of medications were paracetamol and opioid analgesics (n=8) followed by opioids, COX2 (n=2) and NSAIDs (n=2) respectively.

Table 9: Pain medication

Medication	Regular medication (n=102)	Additional medication (n=16)
Paracetamol	31 (13.3%)	2 (0.8%
NSAIDs	10 (4.1%)	1 (0.4%)
COX2 Inhibitors	25 (10.3%)	0
Co-Codomol	15 (6.2%)	0
Opioids	18 (7.4%)	13 (5.4%)
Medicinal	1 (0.4%)	0
Other	2 (0.8%)	0

4.5.1.2.3 Participant reported haemarthropathy

The site and distribution of patient-reported haemarthropathy are presented in Figure 8.

Patient-perceived haemarthropathy was reported by all 243 patients.

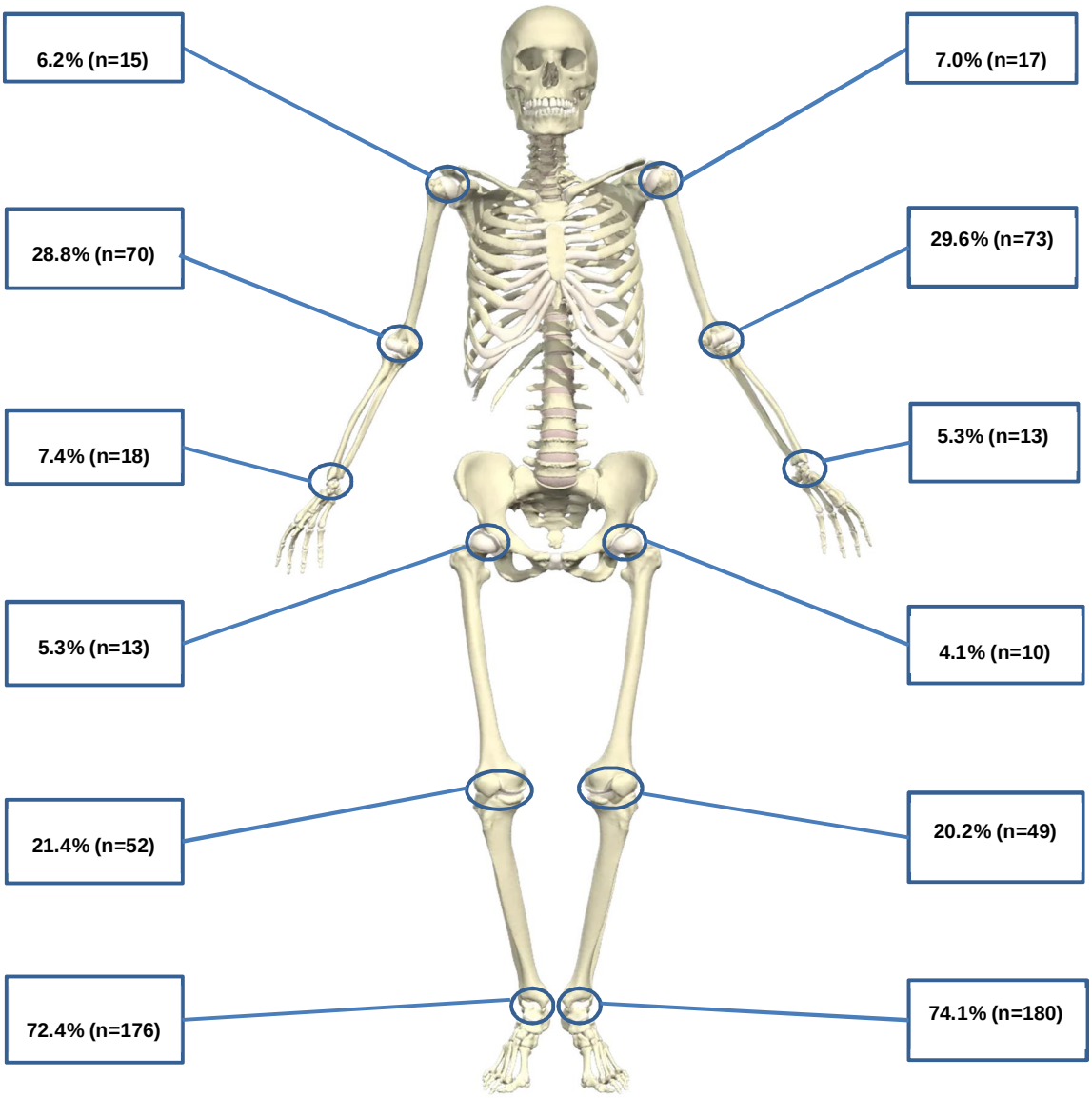


Figure 8: Distribution of patient-reported arthropathy

The distribution of patient-reported arthropathy was similar across the left and right sides of the body. Left and right ankles were the most commonly affected joints, followed by elbows and knees. At the ankle, 117 (48.5%) patients reported bilateral ankle arthropathy, 29 (11.9%) bilateral elbows, followed by 10 (4.1%) wrists and four (1.6%) hips. The shoulders were the only joints where bilateral arthropathy was not reported.

4.5.1.2.4 Ankle HJHS

Ankle HJHS was available for 202 and 199 patients for the left and right ankles respectively and are presented in Table 10. Median HJHS at the ankle were higher in severe haemophilia A patients. Across both haemophilia severities, patients treated on-demand had higher scores, indicating worse ankle haemarthropathy. Moderate prophylaxis groups had higher HJHS, although the haemophilia B group had low numbers of patients. Median on-demand treatment in moderate haemophilia A was relatively low indicating less effect of treatment on the regime in the management of moderate disease.

Table 10: Ankle HJHS

Type	**Haemophilia A**				**Haemophilia B**			
Severity	**Severe**		**Moderate**		**Severe**		**Moderate**	
HJHS Median (IQR)	**Prop (n=133/133)**	**OD (n=18/18)**	**Prop (n=11/10)**	**OD (n=10/9)**	**Prop (n=24/24)**	**OD* (n=3/2)**	**Prop* (n=2/1)**	**OD* (n=1/1)**
Left ankle (n=202)	6.0 (3.0; 9.8)	8.5 (2.3; 11.0)	10.0 (0; 17)	2.0 (0;3)	6.0 (4; 10)	7.5 (-)*	10.0 (-)*	7.5 (-)*
Right ankle (n=199)	5.0 (2.0; 9.0)	7.5 (4; 12)	5.0 (0; 11)	1.0 (0;1)	3.0 (1; 6)	6.0 (-)*	7.0 (-)*	6.5 (-)*

*Prop= prophylaxis, OD= on demand *= ≤3 (n=left ankle/right ankle)*

4.5.1.2.5 Ankle pain-specific location

Ankle pain-specific location was reported by all 243 patients. Across disease, severity, and treatment type, the most common site of pain was the left lateral ankle, with 143 (60.9%) and right lateral ankle 125 (51%), patients indicating pain. Right medial ankle 110 (45%), left medial ankle 118 (48.5%), left posterior ankle 80 (32.9%), right posterior 83 (34.2%), and anterior ankles, right 115 (47.3%) and left 125 (51.3%). Where both left and right ankle pain were pooled by site, the lateral ankles (81, 33.3%) were the most common site of ankle pain followed by anterior, (74, 30.5%) medial (72, 29.6%) and posterior (54, 22.2%) ankles.

4.5.1.2.6 Ankle surgery

Ankle surgery was reported in 95 out of 243 patients. The surgery site was evenly distributed by left (30, 31.6%), right (29, 30.5%) and bilateral ankle surgery (31, 32.6%). Five patients (5.3%) did not indicate side. The most common unilateral procedure was ankle fusion (52, 54.7%), followed by arthroscopic debridement (11, 11.6%), osteophyte removal (4, 3.8%) and open ankle debridement (n 4, 3.8%). Radioactive synovectomy subtalar joint fusion and total ankle replacement were performed each in two patients. An Achilles lengthening z-plasty was reported by one participant. Secondary surgical procedures were recorded in 23 (24.0%) patients. Contralateral ankle fusions were indicated in 14 (61.9%) patients and subtalar joint fusion in three (13.0%) patients. Contralateral ankle surgical procedures; arthroscopic debridement: total ankle replacement, radioactive synovectomy, and osteophyte removal were reported once each, respectively.

4.5.1.3 Clinical Services

4.5.1.3.1 Consultant survey and patient questionnaire responses

Overall, 41 responses were collected from 28 CCC and 13 haemophilia treatment centres (HC) across the UK. Specialist services consultant survey responses are reported in Figure 9. Concerning the specifics of access to clinical care, both consultant survey and patient questionnaire responses are compared in Figures 10-12. Consultant-reported access to specialist services at haemophilia centres was indicated either directly or indirectly in all settings for rheumatology and orthopaedics. Point of care diagnostic US was minimally available, with a total of 19 (43%) centres reporting no access (11 CCC, 8 HC). Consultants at seven (17%) centres had no access to radioactive synovectomy services (3 CCC, 4 HC). Finally, four (9%) centres (3 CCC, 1 HC) had no access to psychology. A total of 13 (31.7%) centres (8 CCC, 3 HC) had no access to two services (US, RS, physiology, routine podiatry), with only one (2.4%) HC without access to three clinical services (routine podiatry, US, RS).

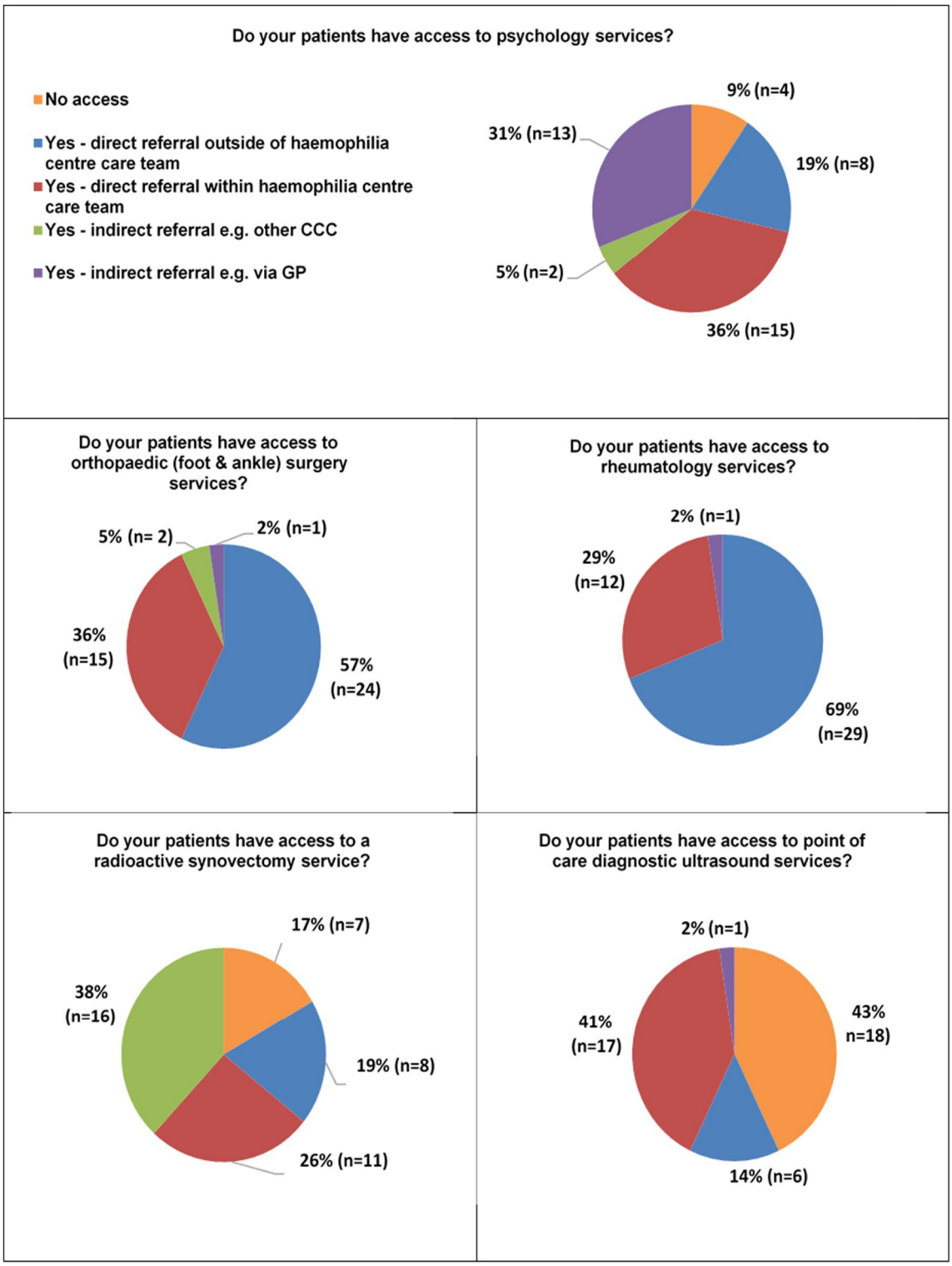


Figure 9: Consultant access to specialist services

Consultant survey (n=42, 100%) and patient questionnaire (n=215, 89%) responses reported access to physiotherapy (Figure 10) at haemophilia centres either directly or indirectly, but 26 (11%) patient questionnaire responses report no access. Access to orthotic services for the provision of devices such as braces and AFOs, commonly used in the management of ankle pathology, were again reported in the consultant survey (n=42, 100%) as accessible either by direct or indirect referral at all haemophilia centres. In comparison, a high proportion of the patient questionnaire responders did not use specialist footwear (n=211, 88%) or foot orthoses (n=117, 51%). Therefore, whilst services are available, patients were either unaware or chose not to access orthotic services.

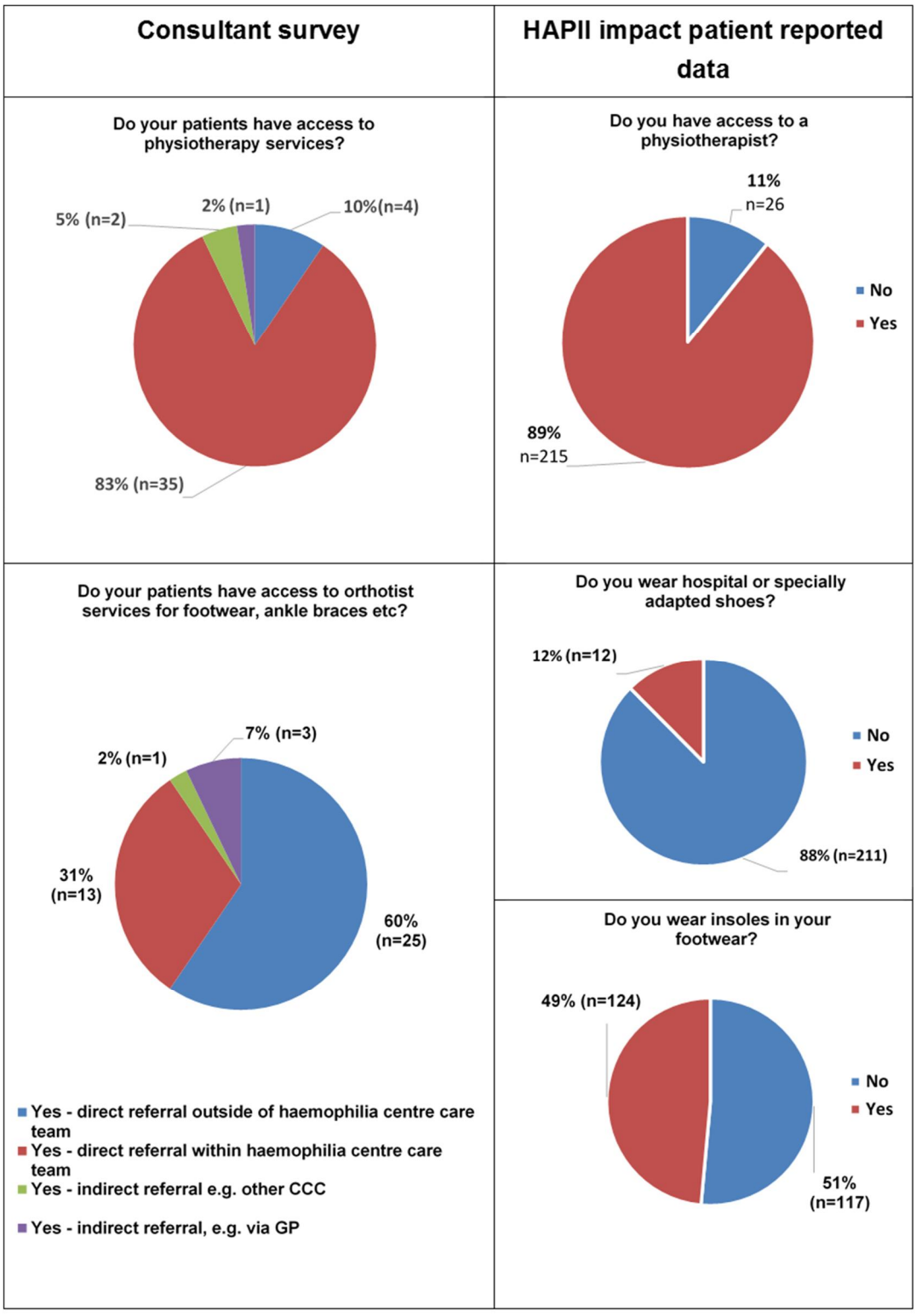


Figure 10: Consultant and participant access to physiotherapy and orthotic services

Access to musculoskeletal podiatry services is presented in Figure 11. A large proportion of the questionnaire patients reported no access to a podiatrist (n=139, 58%). In the proportion that indicated access, 81 patients (34%) were supplied with orthoses. When asked the specifics of what was provided (n=116 responses), 73 patients (63%) obtained their orthoses from the NHS, but 36 patients (31%) used shop-bought devices. A small proportion was supplied by a private podiatrist (n=7, 6%).

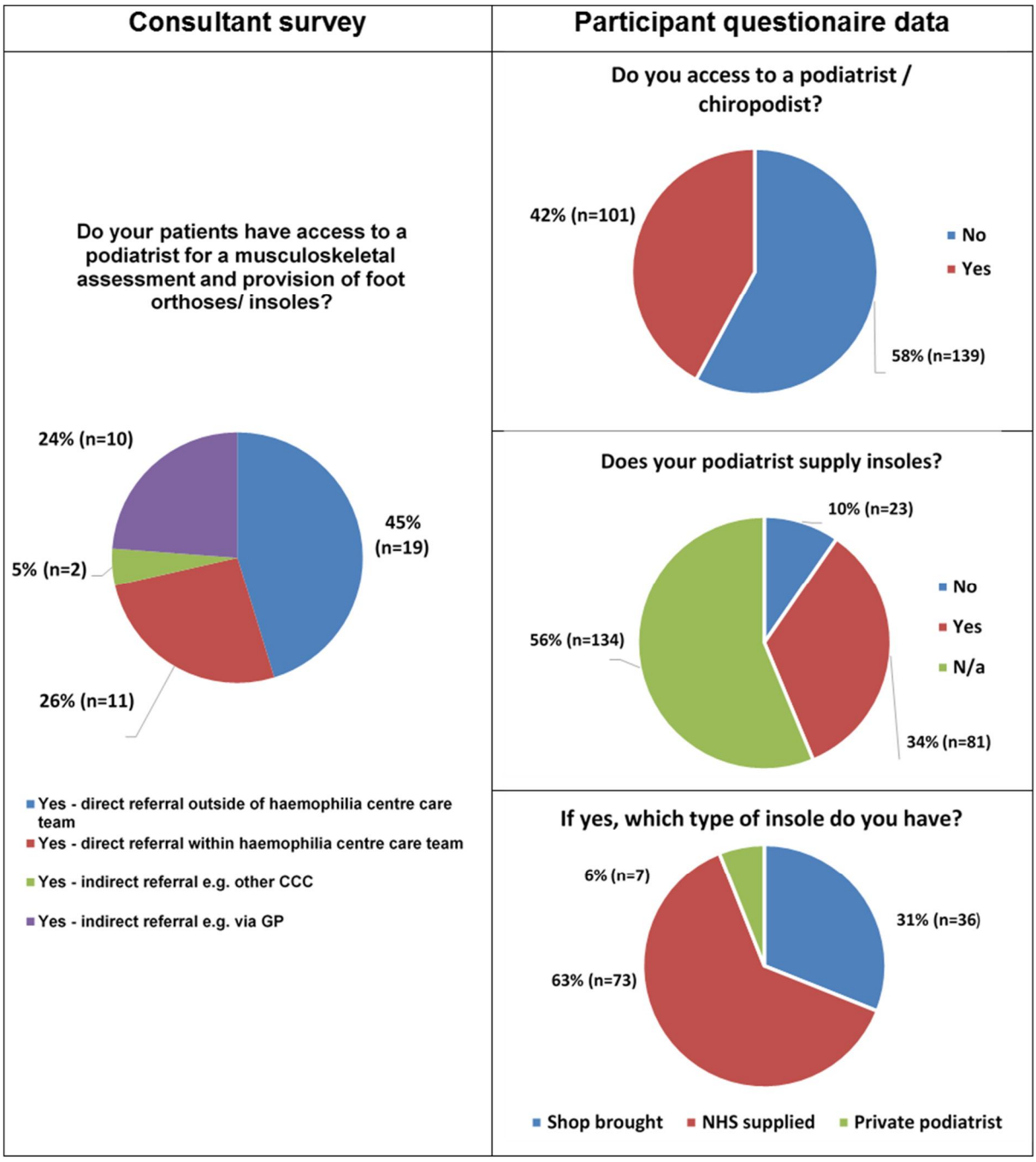


Figure 11: Consultant and patient-reported access to podiatry musculoskeletal services

Access to podiatry for routine foot care is presented in Figure 12. Only four HC reported no access to routine podiatry care, while 133 (57%) patients in the impact questionnaire suggest the need for routine foot care is not a requirement. Only 20 (8%) questionnaire patients received routine foot care.

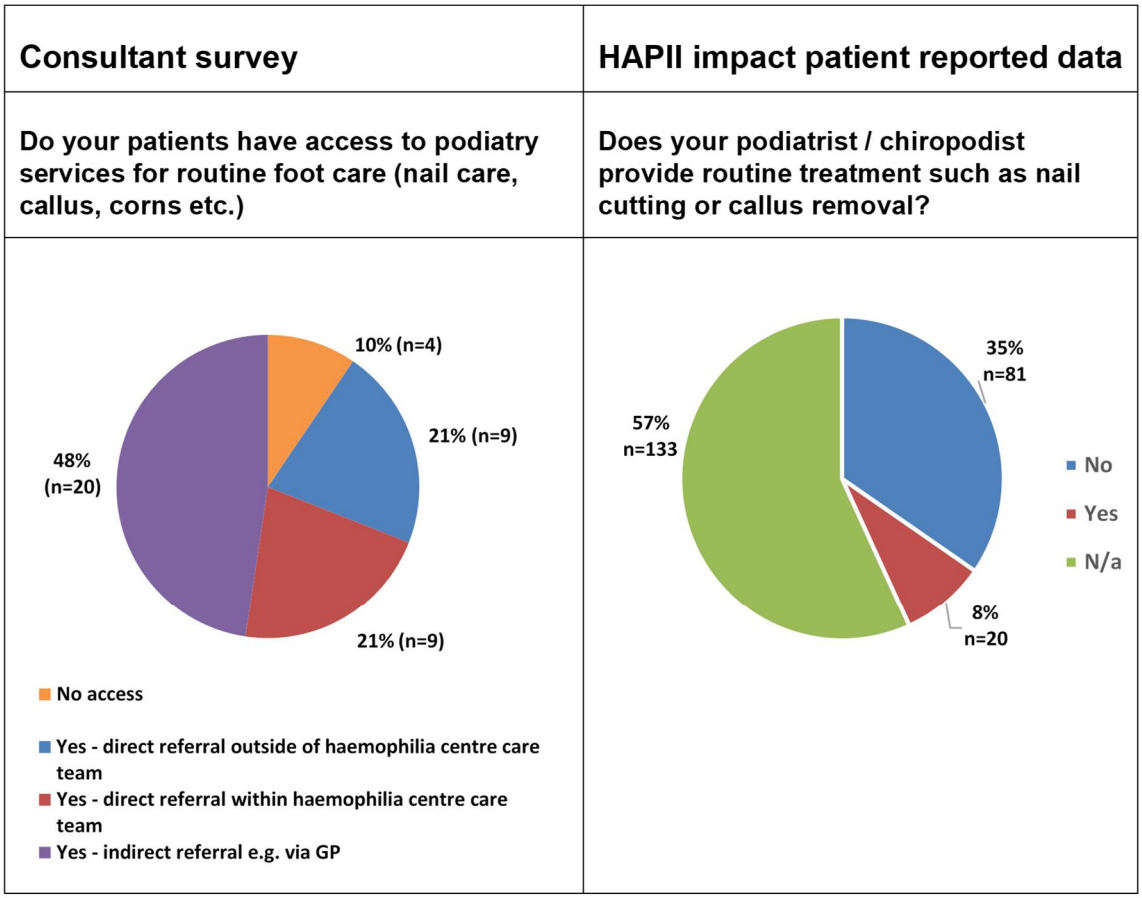


Figure 12: Consultant and participant access to podiatry routine foot care

4.5.1.4 Patient-reported outcome measures

4.5.1.4.1 HAEMO-QoL-A

Total and individual domain scores of the HAEMO-QoL-A are presented in Table 11. The total scores were generally low (100=best health), indicating poor HRQoL associated with ankle haemarthropathy, regardless of haemophilia type, severity or treatment regime.

Table 11: Individual and total HAEMO-QoL-A

Type	Haemophilia A				Haemophilia B			
Severity	Severe		Moderate		Severe		Moderate	
Treatment	Prop (n=164)	OD (n=20)	Prop (n=11)	OD (n=14)	Prop (n=27)	OD (n=3)	Prop (n=3)	OD (n=1)
Physical functioning (mean, SD)	2.41 (0.57)	2.79 (0.59)	2.47 (0.50)	1.78 (0.70)	2.22 (0.45)	2.56 (0.11)	2.56 (0.29)	1.56
Role functioning	1.60 (1.56)	1.69 (1.03)	1.69 (1.20)	0.87 (0.70)	1.43 (1.22)	1.82 (1.41)	2.12 (2.26)	0.64
Worry	1.40 (1.28)	1.20 (1.30)	1.67 (1.30)	0.99 (1.10)	1.32 (1.06)	1.00 (1.40)	1.73 (2.00)	0.00
Consequence	1.50 (1.17)	1.55 (1.39)	1.78 (1.30)	1.30 (1.20)	1.38 (1.21)	2.43 (2.29)	2.38 (2.16)	1.14
Emotional impact	2.80 (0.94)	2.95 (1.26)	2.94 (0.70)	3.00 (1.20)	2.77 (0.84)	2.89 (1.35)	2.50 (0.76)	3.67
Treatment concerns	1.22 (1.24)	1.28 (1.26)	1.97 (1.50)	1.14 (1.30)	1.09 (1.26)	1.22 (1.07)	1.89 (2.69)	0.33
Total Score	10.93 (4.04)	11.46 (4.0)	12.53 (4.70)	9.10 (4.80)	10.20 (3.86)	11.91 (2.27)	13.18 (8.63)	7.33

Prop= prophylaxis, OD= on demand

4.5.1.4.2 MOXFQ

Total and individual domain scores of the MOXFQ are presented in Table 12. Total scores were similarly high across all haemophilia types and treatment regimens (50 to 59), indicating worsening pain and function, except for those with moderate haemophilia B (n=4).

Table 12: MOXFQ (foot and ankle)

Type	Haemophilia A				Haemophilia B			
Severity	Severe		Moderate		Severe		Moderate	
Treatment	Prop (n=164)	OD (n=20)	Prop (n=11)	OD (n=14)	Prop (n=27)	OD (n=3)	Prop (n=3)	OD (n=1)
Walking/standing (Mean, SD)	16.2 (8.2)	18.6 (6.7)	17.5 (7.8)	11.5 (8.1)	16.6 (7.9)	20 (2.0)	17.3 (6.1)	16.0
Pain	10.0 (4.8)	10.0 (4.8)	11.2 (5.2)	7.4 (4.7)	10.2 (5.1)	12.7 (1.5)	12.7 (4.7)	11
Social	5.9 (4.1)	7.5 (3.5)	6.6 (4.2)	3.9 (2.8)	5.7 (4.3)	5.0 (2.6)	7.7 (7.4)	4
Total Score	50.1 (24.7)	56.5 (20.6)	55.1 (24.5)	35.5 (22.6)	50.8 (23.1)	58..9 (4.8)	58.9 (27.5)	48.4

Prop= prophylaxis, OD= on demand

4.5.1.5 Regression analysis

In line with the hypothesis of this chapter, haemophilia characteristics of type, severity and treatment type were not directly linked to worse HRQoL or foot and ankle PROMs.

4.5.1.5.1 HAEMO-QoL-A

When analysed, neither haemophilia type nor treatment type was independently associated with HAEMO-QoL-A total scores, nor were any of the domain scores (Table 13). Haemophilia severity was associated with poorer physical function but was not independently associated with differences in any other domain, and not with the HAEMO-QoL-A total score.

Table 13: Linear Regression Coefficients for HAEMO-QoL-A					
Outcome	**Potential Predictor**	**Unstandardized Coefficients B**	**Sig.**	**95% Confidence Interval**	
				Lower bound	**Upper bound**
Total HAEMO-QoL-A scores	**Haemophilia type**	-0.42	0.598	-1.94	1.10
	Treatment type	-0.18	0.817	-1.73	1.37
	Severity	0.06	0.950	-1.75	1.86
Physical function	**Haemophilia type**	-0.15	0.177	-0.36	0.07
	Treatment type	0.13	0.224	-0.08	0.35
	Severity	0.38	0.004	0.12	0.63
Role function	**Haemophilia type**	-0.06	0.769	0.83	1.84
	Treatment type	-0.03	0.877	-0.49	0.36
	Severity	0.27	0.293	-0.46	0.40
Worry	**Haemophilia type**	-0.09	0.707	-0.55	0.37
	Treatment type	-0.27	0.255	-0.75	0.199
	Severity	-0.06	0.825	-0.61	0.49
Bleeding	**Haemophilia type**	0.05	0.831	-0.40	0.49
	Treatment type	0.07	0.769	-0.38	0.52
	Severity	-0.05	0.848	-0.58	0.48
Emotion	**Haemophilia type**	-0.05	0.769	-0.40	0.29
	Treatment type	0.08	0.670	-0.27	0.42
	Severity	-0.10	0.615	-0.51	0.30
Treatment	**Haemophilia type**	-0.12	0.617	-0.58	0.35
	Treatment type	-0.15	0.531	-0.63	0.32
	Severity	-0.37	0.187	-0.93	0.18

4.5.1.5.2 MOXFQ (foot and ankle)

Again haemophilia type, treatment type or severity grading were not independently associated with MOXFQ scores (Table 14).

Table 14: Coefficients MOXFQ (foot and ankle)

Outcome	Potential Predictor	Unstandardized Coefficients B	Sig.	95% Confidence Interval	
				Lower bound	Upper bound
MOXFQ Total score	Haemophilia type	2.10	0.642	-6.79	10.99
	Treatment type	0.10	0.983	-8.97	9.16
	Severity	5.21	0.332	-5.36	15.78
Walking/ standing	Haemophilia type	0.79	0.596	-2.13	3.71
	Treatment type	0.08	0.956	-2.89	3.06
	Severity	2.02	0.252	-1.45	5.50
Pain	Haemophilia type	0.73	0.421	-1.05	2.50
	Treatment type	-0.53	0.563	-2.34	1.28
	Severity	0.32	0.763	-1.79	2.44
Social	Haemophilia type	-0.17	0.824	-1.66	1.32
	Treatment type	0.51	0.508	-1.01	2.03
	Severity	0.99	0.273	-0.78	2.76

4.5.1.5.3 Stepwise regression analysis

4.5.1.5.4 Regression analysis stepwise effect

The final regression models are reported in Table 15. Stepwise regression led to the exclusion of HJHS for left and right ankles for the HAEMO-QoL-A total scores. Treatment IU/kg, HJHS for the left ankle, HJHS for the right ankle and factor product were also excluded from the final MOXFQ model. In the HAEMO-QoL-A NPRS model accounted for 52% of the R-square proportion of variance, where all were significant. In the MOXFQ total scores model, R-square was 73%. In both total scores models, pain over the past 6 months was a significant predictor of worse HRQoL, as was inhibitor status.

Table 15: Stepwise regression analysis final model

Outcome	Variable	Unstandardized Coefficients B	Sig.	95% Confidence Interval	
				Lower bound	Upper bound
Haemo-Qol-A Total score	NPRS six months	0.76	<0.001	0.56	0.98
	Inhibitor status	4.14	0.001	1.68	6.55
MOXFQ Total score	NPRS six months	6.84	<0.001	5.88	7.80
	Inhibitor status	11.39	0.048	0.12	22.65

4.5.1.5.5 Sensitivity analysis

A sensitivity analysis of the subscales of both the HAEMO-QoL-A and MOXFQ was undertaken to establish whether individual domains of the HAEMO-QoL-A and MOXFQ were directly linked to HRQoL and foot and ankle outcomes. Results of the HAEMO-QoL-A and MOXFQ are presented in Table 16 and Table 17 respectively. NPRS over six months was found to be directly linked to all HAEMO-QoL-A and MOXFQ sub-scales indicating NPRS over six months may be a useful indicator of overall HRQoL and worsening foot and ankle outcomes. Specifically, the interpretation indicates that decline

in HRQoL is mostly driven by pain in haemophilia. Inhibitor status (current inhibitor) had a significant effect on role function, worry, bleeding and treatment. This indicates that the presence of an inhibitor, and the associated risk of bleeding, are a significant burden on HRQoL. On-demand treatment and physical subscales were also significantly associated with outcomes, indicating that treatment choice directly affects physical function, a known consequence of treatment regime (on-demand vs prophylaxis).

Table 16: **HAEMO-QoL-A subscales stepwise regression analysis final model**

HAEMO-QoL-A Sub-score	Variable	Unstandardized Coefficients B	Sig.	95% Confidence Interval	
				Lower bound	Upper bound
Physical function	NPRS six months	0.05	0.003	0.02	0.09
	Factor product	-0.50	0.009	-0.08	-0.01
	On demand treatment	0.31	0.013	0.07	0.56
Role function	NPRS six months	0.22	<0.001	0.16	0.28
	Inhibitor status	0.85	0.018	0.15	1.55
Worry	NPRS six months	0.24	<0.001	0.18	0.31
	Inhibitor status	0.79	0.041	0.03	1.55
Bleeding	NPRS six months	0.19	<0.001	0.12	0.25
	Inhibitor status	1.04	0.005	0.30	1.79
Emotion	NPRS six months	-0.11	<0.001	-0.162	-0.06
Treatment	NPRS six months	0.17	<0.001	0.10	0.24
	Inhibitor status	1.36	0.002	0.52	2.21

Table 17: MOXFQ subscale stepwise regression analysis final model					
MOXFQ Sub-score	**Variable**	**Unstandardized Coefficients B**	**Sig.**	**95% Confidence Interval**	
				Lower bound	**Upper bound**
Walking/ standing	NPRS six months	1.85	<0.001	1.50	2.20
	HJHS right	0.23	0.021	0.04	0.43
Pain	NPRS six months	1.40	<0.001	1.22	1.59
Worry	NPRS six months	1.05	<0.001	0.89	1.24
Social	Inhibitor status	2.85	0.011	0.67	5.04

4.6 Discussion

This study used the HRQoL questionnaire and foot and ankle PROMs to understand the impact of haemarthrosis and ankle haemarthropathy in a cohort of severely and moderately affected haemophiliac adults. In addition, a consultant survey was undertaken to understand current access to clinical services within the UK that provide the MDT management of ankle haemarthropathy. This large multicentre study has identified that across the UK, patients with moderate and severe haemophilia A and B have poor HRQoL, and foot and ankle specific health outcomes, regardless of haemophilia type, severity or treatment regime. Findings suggest that pain may be a significant driver of poor HRQoL, physical function and the risk of bleeding, a significant worry to those with an active inhibitor. The management of ankle haemarthropathy is further blighted by the disparity between consultant perceived access to clinical MDT services and patients own experience of access and use.

4.6.1 Patient characteristics

4.6.1.1 Demographics

Demographics of the patients were representative of the severe adult haemophilia population with higher numbers of haemophilia A and B patients. The sample of moderate haemophilia patients (n=29) whilst small provides insight into the effect of haemarthrosis and levels of ankle haemarthropathy. Patients with moderate haemophilia are required to use prophylaxis CFC treatment, only when they experience regular haemarthrosis, however, this sample of patients were near equally split between on-demand (n=15) and prophylaxis (n=14) treatment [29]. Whilst this sample is small it does provide context to an emerging trend that moderate haemophilia, once considered the treatment target for severe disease is associated with high levels of haemarthropathy [29, 256]. The age of patients would class the cohort as older adults, therefore patients would be more likely to have established haemarthropathy. Associated changes in joint function and structure are related to the length of disease and changing approaches to CFC prophylaxis regimes [2, 33, 257].

The BMI scores in this cohort were above the upper limit of normal (25 Kg/m^2) and therefore the majority of patients fell into the overweight category [258]. In people with haemophilia, as well as the general population, there is a rise in the prevalence of obesity with the World Health Organisation estimating a one-third increase in prevalence since 1975 and 39% of adults classed as overweight [258]. In people with haemophilia, being overweight and obese is thought to increase the burden of disease, as well as having an impact on pharmacokinetic CFC dosing [259]. Reduced plasma volume in adipose tissue is thought to reduce the effectiveness of CFC treatment, though exploration of body weight and CFC treatment has been shown to make no difference to FVIII levels or treatment half-life [260]. Although BMI is the most widely recommended method of reporting the incidence of weight and obesity, it does not discriminate between body fat percentage and lean mass [261]. This is particularly relevant in haemophilia were changes in body composition, muscle atrophy and disability limit activities and muscle

bulk [262]. Population studies in haemophilia have identified that those with arthropathic joint and soft tissue changes tend to avoid exercise due to the inherent risk of bleeding, but those who are overweight may compromise joint function and are at a higher risk of bleeding [262, 263]. This chapter broadly supports this notion, but it is unclear whether higher body mass causes worsening haemarthropathy or physical impairment caused by haemarthropathy leads to increased body mass. Regardless, it is clear that addressing weight gain, lifestyle modifications and dietary changes may reduce the impact of haemarthropathy and long term health at the ankle and other commonly affected joints [259].

4.6.1.2 Multi-joint arthropathy

Multi-joint haemarthropathy was a common feature in the cohort, with the ankle most commonly reported followed by the elbow and knee. These findings are not unexpected as this chapter aimed to recruit patients with known ankle haemarthropathy and the distribution at the knee and elbow is cited in multiple studies [9, 53]; these outcomes are similar to those reported in Chapter Three: prevalence study. Patient-reported sites of arthropathy (Figure 8) indicate similar rates of arthropathy to large cohort studies of OA at the shoulders hands and hips with prevalence (95% CI) per 1000 people of 6.74 (2.19, 11.29), 7.13 (2.51, 11.75) and 6.42 (1.93, 10.91) respectively [251]. The age range of respondents in the Keenan *et al*. (2006) population study was older (aged 55-65) than this cohort but with a similar distribution of joint OA. The age of this cohort (42-49 years) suggests that in haemophilia the incidence of OA at other joints occurs at a younger age than that of the general population. Whilst self-reported patient data can be unreliable, it is unclear whether reported younger onset is a result of haemarthrosis specifically, or the indirect effect of changes in the structure and function of multiple joints caused by haemarthropathy at the ankle elbow and knee [9]. This is an important consideration as the focus is generally placed on the common sites of haemarthrosis of the ankles, knees and elbows. This may not be directly related to haemarthrosis, but rather the

consequences of proximal and distal functional and structural joint changes that cause early initiation of joint disease and multi-joint OA [251].

4.6.1.3 Ankle joint haemarthropathy

The clinically detectable changes at the ankle measured using the HJHS indicate advancing haemarthropathy across all haemophilia disease types with the exception of moderate haemophilia A treating on-demand (Table 10). Whilst there is no consensus on the level of haemarthropathy indicated by the HJHS, one radiological study, has explored concurrent HJHS in patients with severe haemophilia A who reported left and right ankle HJHS of 5.0/6.0. When compared to the Pettersson score, a measure of joint damage in haemophilia, an HJHS of 5.0 to 6.0 correlates to moderate to severe levels of haemarthropathy [209]. Whilst HJHS at the ankle joint is only moderately correlated with joint changes, as haemarthropathy progresses the clinical manifestation of ankle joint damage becomes more apparent [209]. High ankle HJHS were reported in the cohort of haemophilia B patients with mean scores ranging from 3.0-10.0 across disease severity and treatment types. Haemophilia B treated by prophylaxis ankle HJHS were comparable to in those with severe haemophilia A, suggesting that ankles are equally affected in terms of clinically detectable haemarthropathy, but findings are limited by sample size. As discussed in Chapter Two, studies of people with haemophilia B report lower incidence of haemarthrosis with fewer complications of joint haemarthropathy [235]. This cohort appears to differ from other cited studies, but again the small sample size (n=34) limits any firm conclusions. Haemarthropathy has been observed in 17% to 77% of patients with moderate haemophilia in population studies in the Netherlands [5, 264]. Low HJHS in moderate haemophilia treated using an on-demand regime are a reflection of current evidence on the effect of bleeding and the need for treatment In the UK [4]. Total HJHS in moderate haemophilia A are similar to those in severe haemophilia A, but no formal observations were made owing to the sample size (n=122); A large proportion of patients did not have an HJHS, limiting the generalisability of the study [4]. Whilst the Scott *et al*. (2019) study reported total HJHS and the cohort in this study only

reported HJHS for the ankles, it does provide support to the case that there are emerging trends of joint disease in the moderate haemophilia population [4, 256, 265]. Prophylaxis regimes are yet to be formally adopted in the treatment of moderate haemophilia. den Uijl *et al*. (2009) recommended that those with moderate haemophilia should start prophylaxis if they have a trough level of less than three and following their first joint bleed up to the age of five [29]. The effect of haemarthrosis at the ankle and subsequent haemarthropathy in this cohort highlights the level of haemarthropathy across all disease characteristics. In moderate haemophilia, there is a need for a better understanding of the population and the potential effect of detectable and non-detectable episodes of haemarthrosis, which results in a decline of joint health.

4.6.2 Impact of ankle haemarthropathy

The primary aim of this study was to identify the impact of ankle haemarthropathy on HRQoL and foot and ankle PROMs. The results indicate that HRQoL and foot and ankle PROM scores are poor in the presence of ankle haemarthropathy in people with haemophilia. Patient characteristics of haemophilia type, severity and treatment regime did not affect HRQoL, with poor total and domain scores of the HAEMO-QoL-A across all patient characteristics. When patient characteristics were analysed as independent predictors of decline in HRQoL, only haemophilia severity in the domain of physical function was significant (0.004, CI .24; 0.629). Therefore having a direct relationship of severe haemophilia and impaired physical function. Findings in this study are similar to other studies of multi-joint haemarthropathy where severity is associated with worse HRQoL. Higher levels of disability associated with loss of joint function and structural change at the ankles, knees and elbows have been reported in severe disease with patients experiencing the worst outcomes related to bleeding, pain and HRQoL [19, 250, 266]. However, patients with moderate and mild disease with lower levels of joint disease have been reported to be less affected [221, 246]. This was not the case in the current study where people with moderate disease were equally affected as those who have severe haemophilia. Although the 29 moderate cases in the current study is a relatively

small sample (n=29) the findings are similar to De Juili *et al*. (2014), who in a much larger sample (n=75) identified that whilst the majority of those with moderate haemophilia have few bleeds or complications of bleeding, a proportion are severely affected by haemarthrosis disability and reduced QoL [29]. In our cohort of moderate haemophilia A, patients treated by prophylaxis reported higher HJHS (Table 10) than those using on-demand treatment. This study suggests that those treating with prophylaxis do so because of a history of spontaneous or traumatic bleed similar to the bleeding profile of severe haemophilia A [5]. Those treated on demand may have fewer clinically detectable joint bleeds or fewer serious ankle haemarthrosis events. Closer monitoring of moderate haemophilia is emerging as a recommendation for this group of patients, leading to changes in treatment regimens [4, 196, 256]. Whist drawing inference from this small sample is done with caution, these findings support the notion that moderate haemophilia should be closely monitored and treated, especially in children with musculoskeletal immaturity exposing joints to a higher risk of long-term complications, including the decline in HRQoL, increased pain and disability [29].

Similar conclusions can be drawn from this sample of haemophilia B patients who were impacted as much as those with haemophilia A in both HRQoL and foot and ankle PROMs. This chapter contradicts reports that people with haemophilia B present with a less severe bleeding phenotype, lower incidence of haemarthropathy and fewer complications [234, 256]. Specifically, haemophilia B is reported to have a lower incidence of bleeding and less joint damage [256]. In this chapter, HJHS of patients with haemophilia B patients were similar to haemophilia A (severity and treatment type) which would suggest that clinical measures of ankle haemarthropathy are the same regardless of haemophilia type. Whilst our results are again to be interpreted with caution owing to the sample size (n=34) It is apparent that where the physical manifestations of ankle haemarthropathy are moderate to severe, the impact on HRQoL is equivalent across disease type and severity. It remains to be established at what point arthropathic joint changes lead to a decline in HRQoL. This chapter has highlighted that measurement of

the physical manifestation of ankle joint disease alone does not fully capture the impact on the patient. Therefore the use of an HRQoL measure such as the HAEMO-QoL-A in clinical practice may help identify a decline in physical health where clinical measures are limited by presentation and examination.

Similar results were reported in the foot and ankle specific total and domain scores of the MOXFQ. Total scores, reported in Table 12 were between 50.1 and 58.9 with higher scores (100 = worst health) across the total domain scores for walking/ standing pain and social interactions. Similarly haemophilia type, treatment and severity were not independent predictors of foot and ankle outcomes, indicating a systemic effect of ankle haemarthropathy. These findings show ankle haemarthropathy directly affects foot and ankle PROMs across the domains of walking/standing and social interaction, regardless of cohort characteristics. Patients with moderate haemophilia treating on-demand HRQoL were less affected (HAEMO-QoL-A total scores 35.5, SD 22.6) for reasons which have been discussed previously. This is the first study to report foot and ankle specific PROMs using the MOXFQ and therefore direct comparison with another haemophilia population is not available. There is limited research that includes foot and ankle specific outcomes in haemophilia studies. Intervention studies assessing the impact of foot orthoses and footwear in the management of ankle haemarthropathy have used the foot function index (FFI) and FFI revised (FFI-R) [14, 175]. In patients with varying levels of ankle haemarthropathy, low to moderate effects of foot orthoses have been reported on pain, activities and disability [175]. The study lacked detail, with a small study sample (n=16) and no clinical measure of haemarthropathy, limiting the comparison to this chapter's findings [175]. Investigation of foot orthoses and footwear effect by Lobet *et al*. (2009) identified low to moderate levels of impact of the interventions using the FFI-R [14]. In both studies, foot orthoses and footwear produced significant reductions in pain [14, 175]. Neither study provided mean data on the FFI domain or total index scores, but both studies reported pre-intervention scores of 22 and 29-32 (FFI-R) respectively indicating low to moderate levels of foot and ankle impact. This is lower than findings in

this chapter (Table 12), but direct comparisons are limited by poor methodology, data reporting and sample size. Studies of preoperative ankle OA have reported MOXFQ scores of 55-60 out of 100, with higher scores indicating worsening foot and ankle pain, walking/standing problems, and social interaction issues as a direct effect of ankle OA [267]. Outcomes in this chapter's cohort are similar indicating people with haemophilia experience foot and ankle outcomes equivalent to people with ankle OA who have ankle fusions and TAR surgery [267]. This chapter has identified that foot and ankle outcomes in people with haemophilia who have ankle haemarthropathy have significant levels of pain and disability equivalent to people with OA immediately before surgery for foot and ankle disease. This thesis chapter aimed to understand the impact of ankle haemarthropathy, and therefore all patients had a consultant diagnosis of ankle haemarthropathy confirmed by diagnostic imaging (x-ray/ MRI). Ankle HJHS scores (Table 10) were between 3.0 to 10.0, but mean SD were as high as 17 indicating advanced end-stage haemarthropathy associated with chronic pain and disability [76]. Whilst there is no agreement as to the level of haemarthropathy indicated by HJHS when compared with radiological scores of joint disease the mean HJHS in this chapter would suggest moderate to severe levels of haemarthropathy [209]. These results show that the presence of moderate to severe levels of ankle haemarthropathy severely impacts foot and ankle outcomes that are driven by high levels of patient-reported pain.

Inhibitor status was significantly associated with the decline in HAEMO-QoL-A and MOXFQ total scores (Table 15). The findings of this chapter suggest that the presence of an inhibitor is a significant predictor of declining HRQoL and foot and ankle outcomes. The development of inhibitors is a major complication of haemophilia and clinically difficult to manage both physically and psychologically [39, 42, 268]. Immune response to CFC significantly reduces drug half-life making standard treatments ineffective resulting in an increased risk of bleeding [39]. The presence of inhibitors is also associated with increased levels of joint arthropathy, chronic pain, long periods of hospitalisation, absenteeism from work and decline in QoL compared to non-inhibitor

patients [268]. Inhibitor status should therefore highlight not only the physical risk of bleeding and disability to the patient but also the potential for a decline in HRQoL and foot and ankle outcomes. Findings indicate that the impact of ankle haemarthropathy is multi-factorial, in the presence of ankle pain and persistent joint bleeding that does not respond to CFC treatment, inhibitor status should be closely monitored to prevent or delay ankle haemarthropathy.

HAEMO-QoL-A physical function domain and on-demand treatment (P=0.13 CI, -0.087; -0.01) were both independent predictors of declining HRQoL. Physical function is severely impacted in the presence of ankle joint haemarthropathy. The walking and standing domain of the MOXFQ and right ankle HJHS were also significant (P=0.021 CI, 0.035; 0.429) with higher HJHS a predictor of decline in the walking and standing domain scores. Data suggests that on-demand treatment directly impacts physical function and consequence of adherence to treatment and regime (prophylaxis, on-demand). Numerous publications have reported the efficacy of prophylaxis on reducing ABR and AJBR and the reduction of haemarthropathy development so the low AJBR in this study is not unexpected [33-36]. Increased bleeding events are associated with increased pain, disability and rapid decline in joint health [33, 36, 246, 257, 269]. Direct correlation between regular prophylaxis and decline in joint health deterioration has also been shown to improve physical and radiological joint changes [270]. Results are consistent with primary and secondary prophylaxis studies that have shown physical function declines at a much faster rate if treated by on-demand CFC. In a large cohort study (n=903) exploring QoL in patients receiving different treatment regimens, significant differences ($p<0.02$) in SF-36 physical domain scores are reported when on-demand treatment (68.4 SE1.54) is compared to prophylaxis (73.5 SE1.95) [11]. In comparison, Collins *et al*. (2010) seminal study of secondary prophylaxis and on-demand treatment in adults (n=22) identified significant reductions in ABR and AJBR but did not find significant differences in total HAEMO-QoL-A scores. Individual domains including physical function improved on prophylaxis but were not significant. Whilst specific scores

were not reported there were reported improvements in those treated by prophylaxis compared to on-demand [2]. Findings in this study indicate that the impact on ankle haemarthropathy is significantly higher when using on-demand treatment and is an independent predictor of reduced HRQoL and foot and ankle physical function. The majority of patients on treatment in the UK are now taking regular prophylaxis, but our results suggest that those who start secondary prophylaxis are more at risk of decline in physical function and therefore should be closely monitored to reduce the impact of ankle haemarthropathy [232].

The significance of right ankle HJHS as an independent predictor of decline in the walking and standing domain of the MOXFQ is consistent with moderate and severe levels of ankle haemarthropathy reported in this chapter. It is unclear why the right HJHS was significant as scores were similar between left and right HJHS, this could be related to limb dominance or could be a data artefact. Difficulties in undertaking ADL where ankle joint haemarthropathy is established is associated with loss of ROM and chronic joint diseases [113]. Functional limitations associated with basic (walking/ standing) and complex (running/ jumping) lower extremity activities have been associated with an increase in age and loss of ROM but not with pain, however, the subgroup was younger than the cohort of patients in this chapter and may not have had the same level of joint changes seen in the impact chapter patients [266]. This contradicts this chapter's findings that ankle pain is significant in the presence of ankle haemarthropathy. The patients sampled in the aforementioned study were classed as arthropathic based on the radiological Pettersson (x-ray) score only, whereas the impact questionnaire patients were recruited based on a consultant diagnosis. Therefore the clinical signs and symptoms of ankle joint haemarthropathy and previous medical history such as episodes of haemarthrosis and pain management would have been considered.

Ankle pain was the most impactful feature across all haemophilia disease characteristics. Measurement of ankle pain using NPRS over six months is an independent predictor (Table 15) of total and individual domains of both primary outcome measures the

HAEMO-QoL-A and MOXFQ and is a significant predictor of decline in HRQoL (P=0.00 CI .559; .978) (Table 16) and foot and ankle outcomes (P=0.00 CI 5.87; 7.79) (Table 17). In this chapter, patients with ankle pain reported over the past six months using NPRS scores between 4.8 and 6.0 on an 11 point scale (0-10) reported in Table 8. Our NPRS ranged from 4.8 to 6.0 across the cohort which is similar to that seen in studies of severe haemarthropathy. A large US survey of the pain experience (n=764) in people with haemophilia who have haemarthropathy reported pain with average persistent pain NPR scores of 4.32/10 (SD, 2.53) in moderate and 4.25/10 (SD, 1.90) in severe haemophilia. Pain was also the most significant contribution to the decline in QoL [271]. The level of haemarthropathy was not reported and whilst the health care models of both countries differ, scores were slightly lower than those reported in this cohort, suggesting this data is representative of severe haemophilia in both chronic and acute pain driven by synovitis and chronic joint disease [271].

These findings, therefore, indicate that the use of NPRS to measure ankle pain over six months may predict worsening outcomes. Pain at the ankle has been identified as the largest contributor to the decline in HRQoL; decline in ADLs associated with multi-joint haemarthropathy accounting for 45.1% of all joint pain when compared to other commonly affected joints [250]. Details of pain at other joints were not recorded in this study, but the patient-reported distribution of haemarthropathy (Figure 8) was similar to other studies where multiple joints are affected, and the prevalence data was reported in Chapter Three. Ankle pain is often problematic in clinical practice, unlike other affected joints the complexities of ankle joint biomechanics means the ankle is subjected to high forces with ground reaction forces up to five times the body weight during the stance phase of gait and restrictions in ankle ROM make offloading the ankle during ADL difficult [14, 72]. The level of ankle pain highlights the effect of chronic ankle joint pain and the impact on HRQoL and foot and ankle specific outcomes. Pain is the most significant feature of ankle joint haemarthropathy and it is clear pain is a significant indicator of worsening HRQoL and foot and ankle specific PROMs. Both the prevalence data

presented in Chapter Three and the primary outcome data presented in this chapter highlight that the ankle is the most impacted joint by haemarthropathy and the effect on HRQOL and foot and ankle outcomes are significant.

4.6.3 Management of ankle haemarthropathy

4.6.3.1 Pharmacological management

The use of CFC for the treatment of mild and severe ankle haemarthrosis resulted in very much improved/much-improved pain following mild and severe joint bleeds respectively (Table 7). Infusion of CFC following haemarthrosis is known to result in rapid bleed resolution and the reduction of pain [272]. The complexities of pain in haemophilia are acknowledged [266], specifically the ability to differentiate between acute haemarthrosis and chronic pain. Patients have been reported to treat episodes of joint pain with CFC as the physical manifestation of joint bleeding declines and chronic joint haemarthropathy and associated pain increase [221]. It is unclear whether the patients in this chapter were treating haemarthrosis or musculoskeletal pain. A period of rest following a suspected haemarthrosis resulting in a reduction in pain is often an indicator of chronic OA pain in haemophilia, but this becomes more difficult to differentiate as haemarthropathy progress [221]. Clinically patients often treat an incidence of joint pain as a suspected joint bleed with extra CFC treatment; if in doubt as to whether a bleed has occurred treatment should be initiated [272]. Patient questionnaire responses to ankle pain response to CFC treatment for a mild and severe bleed were much improved for both mild and severe bleeding, suggesting that in the presence of moderate to severe ankle haemarthropathy it is still possible to differentiate haemarthrosis, and CFC treatment is effective at reducing symptoms [221].

Regular use of pain medication was only reported in 43.7% of patients despite acute and chronic pain being a key feature of our ankle haemarthropathy cohort. These results indicate much lower levels of pharmacological pain management than that of Wallny *et*

al. (2001) who reported 76% of patients took daily medication for chronic joint pain [250]. Paracetamol, Non-steroidal Anti Inflammatory Drugs (NSAIDs) and COX2 selective inhibitors were the most commonly reported form of analgesia. Paracetamol followed by traditional NSAIDs and COX2 inhibitors are recommended as the first and second-line treatment of pain, but with gastrointestinal and cardiovascular comorbidity risk respectively, caution is advised [53]. Strong opioid analgesics for chronic pain in people with haemophilia are recommended were moderate to severe pain persists for up to six months in duration, and with consideration to tolerance and dependency [140]. Opioid analgesics were only used by a small number of patients (Table 9) in this study suggesting opioids are used sparingly. This is in contrast to a recent US study that reported 56% of adults with haemophilia used opioid analgesics for pain. However, US prescribing practices differ greatly from the UK with emerging evidence of over-prescription of opioids and dependency in US cohorts [249, 273]. It is unclear why the other 56% of patients did not use pain medication despite similar NPRS scores. The explanation may lie in the complexities of pain and other contributing factors such as perception, experience and response to pain [272]. It is beyond the scope of this chapter to discuss the complexities of pain, but patients are known to experience pain differently, develop coping strategies to deal with pain such as exercises, massage and physical therapy and distraction techniques or ignoring pain to combat symptoms [268, 272].

4.6.3.2 Surgical management

Ankle fusion surgery was reported in 59 patients with bilateral fusion reported in 14 patients. Rates of surgical fusion of the ankle joint are similar to those reported in other studies of end-stage ankle haemarthropathy [79, 150, 274]. Pain is a significant driver of the decision to undergo joint fusion surgery with significant improvement in pain, QoL and function reported in several small studies [275-277]. Medium to long term follow-up (six to 10 years) studies of joint fusion have reported a favourable outcome in people with haemophilia who report low levels of pain and low complication rates [167, 174]. Medium to long term outcomes studies of haemophilia and ankle joint fusion (n=57)

report VAS of 0.75 (1.3SD) after a mean of 6.6 years (range 1-18 years) post-surgery indicating good pain outcomes [76]. Similarly, assessment of outcomes at 9.4 years post ankle and subtalar fusion report favourable symptoms scores of 94.9 (of 100) [74]. Whilst we could not confirm any specifics of the time of fusion or post-operative complications, the findings of this chapter question the contribution of fusion surgery to pain improvement and QoL. The patients in this chapter may have additional changes to the joint around the ankle such as the subtalar joint, talonavicular and calcaneocuboid which have been impacted by the changes to talocrural ROM. Radiological studies of OA ankle fusion report arthritis at the hindfoot and midfoot with subtalar joint the most common and severely affected (77.5%) therefore the joints adjacent to the fused ankle may decline and become symptomatic [278]. In haemophilia, the subtalar joint is reported to be affected in 50% of cases, therefore, providing context to results [77]. The fusion may have also caused an additional burden to the contralateral ankle which may further explain levels of chronic ankle pain. The biomechanical consequences of fusion are yet to be established, or the effect on lower limb kinetics and kinematics of the contralateral ankle, which may explain findings in this study that ankle pain and decrease in HRQoL are unaffected by fusion surgery. Further exploration of long term outcomes in large haemophilia cohorts is required to ascertain the impact of ankle fusion in the UK.

TAR was only reported by one patient and whilst TAR failure rates in haemophilia are similar to the general population, patients with haemophilia require surgery at a much younger age owing to the decline in joint health [64]. Therefore the complication of revision surgery, potential for conversion to fusion and pharmacological treatment complications make TAR a less favourable procedure in haemophilia and not commonly performed [171]. Emerging pharmacological treatments such as EHL and BsMAbs may improve long term joint health but their long term effect is yet to be established [225, 226, 241]. Reductions in ankle haemarthropathy and improvements in treatment may therefore allow joint sparing surgery such as osteophyte or arthroscopic debridement. Current ankle surgery procedures require additional treatment and high CFC treatment

levels during and after the procedure increases the risk of complications [8]. Therefore at the ankle, haemarthropathy surgical options remain limited.

4.6.3.3 Pharmacological treatment

Patients were asked to provide characteristics of treatment dose and regime. Prophylactic regimens were used by a large proportion of patients with only 15.7% (n=38) using on-demand treatment, of whom 6.2% (n=15) had moderate haemophilia. It is unclear whether primary or secondary prophylaxis was initiated by patients in this chapter and details were not collected as part of the patient questionnaire. The mean age of patients indicates it would be more likely that prophylaxis was started after the second joint bleed or over the age of five, increasing the likelihood of worsening arthropathic joint changes [31, 246]. Secondary prophylaxis in adults has been shown to significantly reduce ABR and AJBR. Collins *et al*. (2010) reported that in adults who were previously treated on-demand, the initiation of secondary prophylaxis over 12 months resulted in significant reductions in joint bleeds (15.0 (11-26) to 0 (0-3)) [2]. Therefore starting prophylaxis in adulthood is still effective at reducing haemarthrosis. In this chapter, ankle joint bleeding with low ankle AJBRs was reported across all disease types. The presence of established joint haemarthropathy has been reported to “burn out” as the levels of joint disease become chronic and the rates of joint haemarthrosis decline [23]. Therefore the level of haemarthropathy in the prophylaxis group explains the low levels of haemarthrosis in this chapter. Reporting of historical AJBR and ABR at the ankle or other commonly affected joints were beyond the scope of this chapter.

Treatment doses per kg were within the UKHCDO recommendation for prophylaxis, but studies of European and UK treatment regimens have suggested that lower IU/kg may indicate under treatment [3, 4]. It is difficult to draw inference from our data due to the absence of trough levels which provide a measure of the participant’s empty level before CFC treatment [1]. Centres were asked to provide trough levels, but how trough levels are taken before treatment, or “empty” may not have been consistent and therefore

misinterpreted. SHL treatment was used by 45.3% (n=107) of haemophilia A patients and a larger proportion of all patients used EHL (50.93%, n=120) in our cohort than the previously reported data in prevalence chapter three of 30%. Our data was collected over a longer period (2018-2020) than the chapter three prevalence data (2018) and therefore the likelihood of access to EHL would be higher, with more patients moving onto EHL products. The use of EHL products has been reported to increase trough levels by 1.6 to 1.8 times that of an SHL and increase trough levels by 20% to 50% with higher trough levels [242], therefore reduce treatment burden and improve HRQoL but this chapters data does not support this, nor the improvement of patient outcomes [49, 224-226].

Treatment of joint bleeds in our cohort presented in Table 6 was within UKHCDO guidelines on acute and chronic joint bleeding of 25-30 IU/kg for haemophilia A SHL and EHL products and 40-60 IU/kg for haemophilia B [13, 43]. The number of days treated was relatively low for both mild and severe incidents, with treatment days of 1-2 for a mild bleed and 3-6 for a severe bleed. During a suspected joint bleed, patients are clinically advised to continue CFC treatment until the pain subsides [43]. Our findings suggest that this is a relatively short period for mild and severe joint haemarthrosis. Diagnostic studies of MSK ultrasound have shown that blood within the joint is present for several days after the initial pain has subsided [145]. Even low levels of blood contained within the joint continues to cause a decline in joint health as well as the inflammatory effects of haemosiderin burden and pro-inflammatory cytokines and proteases [53]. Whist our cohort had moderate to severe ankle haemarthropathy, the use of pain as a marker for treatment of joint haemarthrosis may lead to CFC under treatment. Likewise, it is a balancing act between the effective use of bleed dose CFC and the long term consequence of under-treatment of haemarthrosis. Low-level bleeding has been proposed as a mechanism by which joint health continues to decline [52, 240]. Whilst our study did not ask specifically about treatment following the subsidence of pain,

the treatment length does raise concerns around patient perceptions of treatment length and the risk of ongoing joint damage despite adequate treatment regimes.

4.6.3.4 Access to clinical services

Consultant survey data identified general access to all complementary MSK services associated with the management of haemophilia and joint pathology. Orthopaedics, rheumatology, and AHP services were by direct or indirect referral within haemophilia centres nationally. Only a small number of centres were unable to access specific services (Figure 9) such as point of care ultrasound, radioactive synovectomy and psychology services. This is consistent with data recently published in the Care Quality Review of Inherited and Acquired haemophilia and other Bleeding Disorders Programme 2019/2020 on behalf of the UKHCDO [12]. Access to diagnostic and point of care MSK ultrasound was the most common service with limited or no access by consultants at participating centres. This finding is of particular importance as the emergence of new pharmacological treatments reports better haemostasis and declining AJBR and ABR [241, 279]. It is unclear as to the impact these pharmacological treatments will have on early and established haemarthropathy, however, MSK ultrasound has the potential to monitor joint health as a potential treatment outcome [280, 281]. MSK ultrasound is particularly sensitive to detecting soft tissue pathology associated with haemarthropathy, but at the talocrural joint is limited by access to the joint and the inability to detect subchondral bone changes [282, 283] Whilst limitations are acknowledged, in the monitoring of early disease synovial changes and cartilage make ultrasound a cheap and reliable method of monitoring of joint health and use in clinical practice may improve patient outcomes as well as decrease the impact of disease by timely assessment of joint pain and disability [280].

The consultant survey reported direct or indirect access to orthotics, physiotherapy and podiatry services, but patient responses in the impact study were somewhat different. Access to physiotherapy forms part of the UKHCDO management guidelines [12, 13]. In

the consultant survey, physiotherapy access was reported at all centres, but 11% (n=26) of the impact patients reported no access to a physiotherapist. Despite access improvements, there are still centres that have no full time access to a haemophilia specific physiotherapist and therefore patients may not feel they have access to specialist physical therapy. Physical therapy in haemophilia has been shown to reduce pain and provide expertise in the management of bleeding disorders [284]. Access to adapted footwear and foot orthoses by patients were vastly different to service access indicated by the consultants (Figure 10). Adapted footwear and foot orthoses were not worn by 88% and 51% of patients respectively. Lobet *et al*. (2012) reported good patient satisfaction when using bespoke footwear and casted foot orthoses but failed to identify specifics of the satisfaction questionnaire which may have provided details of contributing factors such as comfort, compliance and acceptability [14]. Patient satisfaction has been identified as high when accessing combined podiatry and physiotherapy services for the provision of footwear [15, 16]. The combined approach to the management of haemarthropathy is positivity associated with improvement in pain, reduction in AJBR and improvement in QoL [15]. Access to a podiatrist was again reported either by direct or indirect referral in UK CCC and HC (Figure 11). Findings indicate that common MSK services provided by a podiatrist are not accessed by patients with ankle haemarthropathy. Access was limited to less than half of patients, with only 34% of patients supplied with foot orthoses. Specifics of foot orthoses provision also indicate that the majority of patients were supplied with foot orthoses by NHS services, but 31% used shop brought orthoses. It is unclear as to why patients used shop brought insoles. Access to orthotic services by either podiatry or orthotics might not be available or poor satisfaction from previous interventions with patients often attending clinics with a bag of previously issued foot orthoses. It may simply be that over the counter orthoses often found on the high street exert their action by providing a cushioning effect and this is enough to provide some form of comfort. The use of combined podiatry and physiotherapy services have shown good patient satisfaction in the management of

ankle haemarthropathy and the provision of foot orthoses in the UK haemophilia cohorts [15, 16]. The clinical needs of patients with ankle haemarthropathy and multi-joint haemarthropathy however are unknown and require further investigation.

Although access to routine podiatry foot care services was available at HC (90%, n=38 centres) for callus debridement and nail cutting, a large proportion of patients (57%, n=133) deemed access as not applicable. Findings suggest that the requirement for routine foot care is not a priority for those with ankle haemarthropathy with only 8% of patients receiving regular foot care. There is no published evidence for the need for foot care in haemophilia, but the progressive plantarflexion deformity and evidence of increased forefoot pressures combined with axial joint deformity at the elbows and knees may limit the ability to self-care [176]. This is typically seen in people with RA where the loss of hand strength and deformity prevent self-care and foot deformity result in the build-up of painful callosities [210, 285]. Whilst multi-joint haemarthropathy is a common feature of the disease, findings suggest that the level of disability reported in this cohort is not sufficient to limit self-care, or may indicate that patients rely on family members to provide foot care.

Research in RA and OA have shown that patient education, regular foot assessment and foot care services improve pain and QoL but to date, there is no published data in haemophilia cohorts [286, 287]. Findings from this study highlight the need for further research to determine the provision of routine and musculoskeletal foot and ankle care required in the management of ankle haemarthropathy. Both modified footwear and foot orthoses have the potential to improve HRQoL and foot and ankle PROMs. However, in a condition characterised by haemarthrosis and bleeding, the mechanism by which the intervention exerts its clinical effect should be established before a full randomised control trial in the haemophilia population.

4.6.1 Limitations

The limitations of this study are acknowledged. Self-reported data has been cited as unreliable with the potential to overestimate specific joint pathology. It relies on patients' interpretation of their condition, however, data presented here is similar to other studies of multi-joint OA and HRQoL in haemophilia and therefore provides assurances to the quality of data [5, 251]. Haemophilia is a life-long condition, therefore they are typically aware of their joint health. Efforts were made to reduce over-reporting by providing details for both the patient and clinician to complete. The small number of patients with haemophilia B and moderate haemophilia included in this study means specific results should be interpreted with caution. This is a difficulty in rare diseases and whilst the number of patients is small, it does highlight emerging issues in the impact of ankle haemarthropathy outside of severe haemophilia A. The small number of moderate haemophilia patients provides further evidence to the effect of moderate haemophilia on joint health status, recently reported in haemophilia literature [5, 29, 265]. Recent advances in treatment have seen people with severe haemophilia without inhibitors grant access to the uses of BsMAb treatment with equivalent factor levels of 20-30% and show promising reductions in ABR, AJBR and treatment burden [225]. Treatment is not currently licenced for use in those with moderate haemophilia, but those affected by high bleed rates and declining joint health may become eligible if evidence of standard and extended half-life therapies.

4.6.2 Conclusion

In the presence of ankle haemarthropathy HRQoL is poor and foot and ankle PROMs are significantly affected regardless of haemophilia type, severity or treatment regime. Pain is the main driver for decline and those with ankle haemarthropathy have high levels of chronic pain. Findings from this study indicate that the assessment of ankle pain using NPRS over six months is directly linked with worsening HRQoL and foot and ankle PROMs. The management of ankle haemarthropathy appears to be inadequate with the disparity in the pharmacological management of pain and bleeding events and non-pharmacological management. Whilst UK CCC report access to a range of MSK services, patients' engagement with mechanical interventions such as footwear and foot orthoses is very low. Further research is needed to understand contributors to decline in HRQoL, management of pain and better quality research to understand how mechanical interventions such as modified footwear and foot orthoses may improve HRQoL. The multi-joint nature of haemarthropathy means that understanding the effect of an intervention on the ankle could potentially lead to unwanted proximal compensation in kinetics and kinematics. Likewise, where modifications to footwear are multi-faceted the effect of individual and combined components provides insight to effect. Therefore before future studies in a haemophilia population, the mechanism of action of interventions should be undertaken in healthy patients to reduce risk to joint health.

Chapter 5 - A mechanism of action study to explore the individual and combined components of the Leeds Ankle Stabilising Enhanced Rocker (LASER) intervention

This chapter establishes the mechanism of action of the LASER intervention. Gait analysis was used to quantify the kinetic and kinematic effect of footwear on the lower limb. Modified footwear can change the kinetic and kinematic profile of the ankle and lower limb joints during gait. The kinetic and kinematic effect of the LASER intervention on the ankle and other lower limb joints was explored in terms of it its individual components and all components combined. The mechanical effects of the intervention on the ankle joint moment of force and range of motion (ROM) were measured in a normal healthy population to avoid exposing patients at risk of joint bleeds to poorly understood mechanical forces.

5.1 Introduction

Ankle pain and osteoarthritis (OA) affect 12% and 4%, respectively in the UK population [288]. Whilst primary OA is uncommon, post-traumatic OA accounts for 70% of symptomatic ankle arthritis, caused by a malleolar fracture and ligamentous injury [288]. Less common causes include inflammatory and crystal, infection and neuropathic arthropathy [288, 289]. In contrast, patients with severe haemophilia have a population incidence of 20% of ankle OA and significant patient-reported pain and disability related to the incidence of haemarthrosis [9, 248]. A single significant episode of haemarthrosis or repeated minor incidents leads to joint health damage by means of reactive synovitis, cartilage haemosiderin deposition and changes to the subchondral bone resulting in permanent damage and structural change and haemarthropathy [60, 69, 290]. The ankle is the most common site of joint health decline and pain as identified in Chapters Two and Three. Pathological changes to the ankle joint result in lower joint stress tolerance when walking as ankle joint haemarthropathy progress [136]. Recently a small study

(n=3) conducted by Talbott *et al*. (2020) investigated changes in contact pressures of the talus using non-weight-bearing MRI with the segmentation of bone, cartilage (n=14 images) and bone cysts. Cyst formation in the talus increased contact pressures by 66% in the talus and 16% in overlying cartilage. If both the tibia and talus are affected then forces are shown to increase by 125% and 120% respectively with a 140% increase in pressure exerted on cartilage [70]. This study, whilst small and experimental rather than definitive, provides context to the functional and structural changes observed clinically at the ankle joint [70]. Sub-optimal condition of bone caused by damage to the articular cartilage and subchondral bone cyst formation results in instability and ultimately joint failure, with those patients in the third decade of life reporting a reduction of 80% ankle joint range of motion (ROM) and significant pain and disability [290]. Ultimately the failure of the ankle joint leads to changes in the ability to continue activities of daily living (ADL) and significantly impacted health-related quality of life (HRQoL) and foot and ankle outcomes identified in Chapter Three.

Progressive destruction of the ankle joint leads to changes in the kinetic and kinematic profile of the lower limbs [18]. During the gait cycle, the foot makes contact with the ground, the ankle joint acting as a fulcrum to allow forward progression of the limb; a process referred to as the ‘anatomical rocker’ [92]. In haemarthrosis of the ankle, gait changes occur at all phases of the anatomical rocker, resulting in a significant reduction in ROM, and gait efficiency [18]. Typically changes in joint structure and function described above and loss of ankle dorsiflexion required for normal walking leads to gradual loss of the normal rocker function of the ankle, significant disability and changes to kinetics and kinematics of the proximal joints of the lower limb. When the anatomical rockers of the heel, ankle and forefoot are impeded by pathological changes such as the structure and function changes reported in ankle haemarthropathy, modified footwear may substitute to facilitate movement during the stance phase of the gait cycle [187, 188]. Modified footwear is commonly used in the management of conditions such as diabetes and RA, to prevent ulceration and improve mobility and function in several

conditions associated with impaired walking and orthopaedic deformity [188-190]. However, there is little published data on the benefit of modified footwear in haemophilia and ankle haemarthropathy, despite the ankle being the most affected joint [14].

Rocker profile shoes are the most common footwear modification used in the management of diseases of the foot and ankle to facilitate motion and redistribute foot pressures [194, 291]. The majority of research on rocker profile footwear concentrates on the offloading and redistribution of pressure associated with the occurrence of diabetic foot ulceration [188]. In the management of ankle OA, the use of rocker profiled shoes has been shown to facilitate change in sagittal plane kinematics by reducing the plantar/ dorsiflexion at the ankle joint where the function is either impeded by pathology or lost by fusion [115, 188, 292]. In haemarthrosis, a rocker profile shoe has the potential to compensate for the reduction in ankle ROM [188]. A heel-toe rocker whereby a negative heel rocker is used in combination with a forefoot rocker has been suggested as the most appropriate configuration in the presence of ankle OA or where ankle ROM is impeded [188, 192]. Kinetic and kinematic changes have been observed at the ankle joint when using a double rocker (rearfoot and forefoot) shoe.

The study by Long *et al.* (2009) of rocker soled footwear in healthy controls (n=40) reports that use of a double rocker sole increased dorsiflexion at midstance, but as the ankle rocker progressed to through to the third ankle rocker, dorsiflexion was significantly reduced, although the reductions reported were between 0.61 and 1.25 degrees (P=0.05) calling into question the clinical relevance of the ROM change [187]. The change reported in dorsiflexion was small, but in ankle haemarthropathy, this small change may reduce the risk of further trauma to the joint and pain associated with osteophyte formation and synovial hypertrophy at the joint margins [293].

Whilst the results should be interpreted with caution owing to the use of a single marker to calculate ankle kinetics, Long *et al*. (2009) did report reductions in plantarflexion

moment from midstance through to toe-off (P=0.01) [187]. Findings indicate the potential to reduce the mechanical burden at the ankle joint by reducing the ROM and moments during all three ankle rockers. This is particularly relevant to ankle haemarthropathy where the gradual loss of ankle ROM in combination with joint pathology exposes the joint to the risk of trauma, haemarthrosis and pain [293]. [135]. Evidence supports the benefit of a double rocker shoe especially in ankle haemarthropathy where changes in both ankle kinetics and kinematics occur ankle joint disease progresses [135].

A smaller study (n=17) of healthy controls investigated a double rocker soled shoe, but with a different short rocker apex point (50% vs 60%). Arazopour *et al.* (2013) [193] reported a reduction in terminal stance dorsiflexion of 9.2 degrees when compared to a standard shoe and a sagittal plane ROM change of 9 degrees. Arazopour *et al.* (2013) [193] found a significant change (p0.023) in the inversion of the ankle by a mean of 10 degrees (SD 4.4) during second double limb support. Likewise, a significant increase of 1.25% (P=<0.05) was reported for external foot rotation. Both studies support the use of a double rocker or heel-toe rocker in the management of ankle OA and arthrodesis, but at the sacrifice of frontal plane motion which increased in both studies. Whist, it is unclear how these finds translate to a pathological cohort, they have potential implications for use in clinical practice, although the authors acknowledge this may lead to instability and a reduction in balance and changes in foot pressures. Both studies acknowledge limitations in methodology and the recommendations for further investigation. Firstly, the collection of in-shoe kinematics to include markers attached directly to the foot or videofluoroscopy to quantify movement of the foot with the shoe. Secondly, the use of a rocker sole in combination with additional modifications such as the SACH [187, 188, 193]. The use of a rocker sole appears to have the potential to change ankle kinetics and kinematics, but the lack of cited research on the effect of modified footwear in the management of those with haemophilia and ankle haemarthropathy indicates a need for further investigation of the mechanical effect in combination with other footwear modifications.

The solid ankle cushioned heel (SACH) modification is designed to allow a normal heel strike during the stance phase creating a pseudo-plantarflexion moment by deformation under loading forces. This is particularly beneficial where ankle ROM is impeded such as talocrural joint OA [192]. The benefits of a SACH have been reported by Wu *et al.* (2004) when using a “spongy” SACH in combination with a forefoot rocker at 60% of a shoe in healthy males [194]. The SACH increased dorsiflexion/plantarflexion at the hindfoot in relation to the tibia (30.2° (SD 5.9°) vs 24.2° (SD3.0°)) when compared to a traditional shoe. The five-degree increase in ROM was identified as mechanically beneficial for patients with ankle pathology or arthrodesis where ankle ROM is impeded. An increase in eversion angle of 3.8° occurred in the frontal plane, a potential compensatory effect that led to a rapid increase in peak plantarflexion at the hindfoot during stance. The author reported that participants thought that the SACH did not provide enough cushioning, nor did it feel thick enough, although no formal PROMs were included. Large magnitudes in the rearfoot inversion may suggest the material used in the spongy SACH deformed too rapidly under load. Details of the SACH material were not reported and may provide more insight, but comments and results suggest a material that gradually deforms under load may be more suitable.

The use of modified footwear has the potential to delay mechanical joint changes, improve reported pain, QoL, kinetic and kinematics in patients with haemophilia and associated ankle haemarthropathy. To date, there is little evidence to support changes in practice or management guidelines. Therefore research in ankle haemarthropathy must establish the mechanical benefit of such adapted footwear before clinical trials. In clinical practice, modified footwear is rarely used in isolation, with foot orthoses used in parallel to also control how the foot interacts with the shoe [188].

In-shoe orthoses, casted insoles and functional foot orthoses (FFO) describe devices that exert or change forces and pressures at the shoe foot interface [113]. Evidence supports the use of in-shoe foot orthoses and FFO in the prevention of foot deformity and provides stabilisation in inflammatory arthritis and the management of the diabetic

foot, but evidence in ankle haemarthropathy is lacking [17-19]. The research was undertaken by Slattery & Tinley (2001) reports significant improvement in foot pain and reduced incidence of bleeding in a group of 16 haemophilia A patients using FFO [294]. Likewise, the use of heel cushion insoles has been reported to improve patient-reported pain and disability, but provide no functional control and where instability of the ankle joint occurs [179]. Jorge *et al.* (2006) reported that the use of FFO produced a significant reduction in spontaneous joint bleeding (P=<0.001), though the type of FFO used provided cushioning action only and was investigated in combination with an ankle brace, potentially confounding the individual effect of the cushioning orthoses [176]. Few studies have investigated the kinetic and kinematic effect of FFOs in haemophilia and blood induced ankle arthritis. Lobet *et al.* (2012) reported little effect of casted high-density polyethene anti-pronatory casted orthoses on ankle biomechanics in patients with haemophilia and ankle haemarthropathy. When orthopaedic insoles were prescribed in combination with a bespoke orthopaedic shoe, little effect was reported either with or without the insole but kinematics were measured using markers mounted on the outside of the shoe, not the skin, a known source of error in gait analysis [295]. Studies have now shown that shoe-mounted markers lead to an underestimate of the ankle kinematics which is essential to calculating joint kinetics [129, 296]. Specifically, comparisons of in-shoe vs shoe-mounted markers have reported significant (P=<0.001) under-reporting of the calcaneal ROM of 5.9 degrees in the sagittal plane, and 1.6 degrees in the transverse planes [125]. Similarly, a comparison of shoe-mounted vs skin mounted markers have reported significantly greater ($p<0.05$) coronal plane peak ROM (3.16°) and peak eversion magnitude (5.11 degrees s^{-1}) [124]. Further investigation using in-shoe measuring techniques such as those described by Bishop *et al.* (2015) is required to appreciate the mechanical effect of FFOs and orthoses in combination with modified footwear in the management of ankle haemarthropathy [126].

In the management of ankle pathology, the LASER intervention, a modified military boot, with a rocker sole and SACH (details described in 5.3.5.3) has been used clinically at

the Leeds CCC to manage ankle haemarthropathy for the past 12 years. Audit data obtained from eight adults diagnosed with haemophilia using the LASER intervention reported an improvement in patient-reported pain and disability scores by 18.5%, and a reduced incidence of ankle bleeds from 11.4 to 2.2 per patient over 12 months [15, 297]. Whilst the individual and combined boot modification and FFO have been investigated, the design of the LASER intervention use of a modified SACH heel in combination with a “heel-toe” rocker profile and a military boot has yet to be explored. Therefore before a study is undertaken in a pathological patient group such as blood induced ankle arthritis ankle the kinetic and kinematic effect of the individual and combined components of the LASER intervention requires the establishment of the mechanism of action.

5.1.1 Study aims

The specific aims of this chapter are:

i. To determine whether a bespoke cluster marker wand is suitable for the collection of in-shoe foot and ankle kinematics.
ii. To compare the accuracy of foot vs boot-mounted gait markers in the collection and reporting of kinematic gait data.
iii. To investigate the biomechanical properties of the LASER intervention when compared to a standard sports trainer in normal volunteers.
iv. To investigate the effect of the LASER intervention on the kinetic and kinematic profile of the lower limb in normal volunteers.

5.2 Pilot study

A pilot study was performed to determine the most appropriate data collection methods for acquiring lower limb kinematics whilst participants wore a military boot used as part of the LASER intervention.

5.2.1 Introduction

The use of carefully modified shoes in biomechanical research has shown comparable repeatability to studies employing barefoot conditions with the advantage of a more realistic clinical application in the collection of multi-segment foot kinematics using surface-mounted markers in healthy volunteers [127, 131]. The bespoke shoes used in past research for in-shoe, skin mounted markers are minimal in the structure of the upper and sole units, a limitation in both studies. The military boot used in the LASER intervention is however a semi-rigid military boot that fastens above the ankle, and therefore significantly more structured than previously investigated footwear [127, 131]. The collection of foot and ankle kinematics requires the use of boot-mounted markers or foot mounted cluster wands, therefore the comparison is required to determine the accuracy of data collection techniques and identify the most reliable method.

5.2.2 Aims

This pilot study aimed to determine the following;

I. Whether a cluster “wand” is suitable for the collection of foot mounted in-boot kinematics.
II. Whether differences in ankle kinematic data are reported between boot-mounted markers set vs foot mounted cluster wand marker set, and which approach should be undertaken in a LASER intervention mechanism of action study.

5.2.3 Pilot study part one: Cluster wand development

Details on in-shoe foot kinematics have been presented in the review in section 2.2.1.1.3, therefore an overview only is presented in this section.

5.2.3.1 Introduction

The measurement of shod 3D kinematics have until recently been captured by shoe-mounted marker sets, but there is emerging evidence that external footwear markers makes assumptions about the movement of the foot within the shoe and therefore incorporates error to kinematics [123]. In a deep shoe such as a military boot, a marker cluster wand is yet to be utilised in-shoe. Cluster wands have been used to obtain hindfoot kinematics in-shoe, however, there are no commercially available marker clusters [20, 131]. It was, therefore, necessary to develop a bespoke cluster wand that can sit on the foot through a window within the shoe. The use of rigid clusters with three or more attached passive markers allows the generation of a virtual marker on the skin surface that can then be tracked during data collection (Figure 13) [298]. A virtual marker can be generated at the cluster wand origin (Figure 13b) using offsets obtained from the known dimensions of the wand.

5.2.3.2 Methods

A cluster wand was created using a 3D printer (3D HUBS, Chicago, US) with 6mm reflective markers placed at the anterior, posterior and superior projections displayed in figure 1a. Three individual kinematic cluster wand positional trials were collected at zero, five and 10 degrees of lateral tilt (Figure 14) using a 10 camera Vicon system (Vicon MX; Oxford Metrics, UK). The cluster wand, measuring 27mm from origin to base was placed in insolation at the gait laboratory origin (Figure 13a) at the Chapel Allerton Hospital (CAH) gait analysis laboratory. Markers were labelled in Vicon Nexus software version 2.6.1 (Vicon, Oxford UK) and exported into Visual 3D software (C-Motion, Germantown, USA). A virtual marker or “landmark” was created by using the three physical markers

on the cluster wand identified as the anterior, posterior and superior markers (Figure 13a). The virtual marker was generated between the anterior (A) and posterior (P) marker within Visual 3D (Figure 13b). A “landmark” was generated defined as the origin marker (O) between the anterior and posterior markers (0.5). A segment was then generated by the anterior, posterior and superior markers with the landmark defined as the centre and another landmark generated at the cluster wand base (B) using methods described in the C-Motion WIKI tutorial [299].

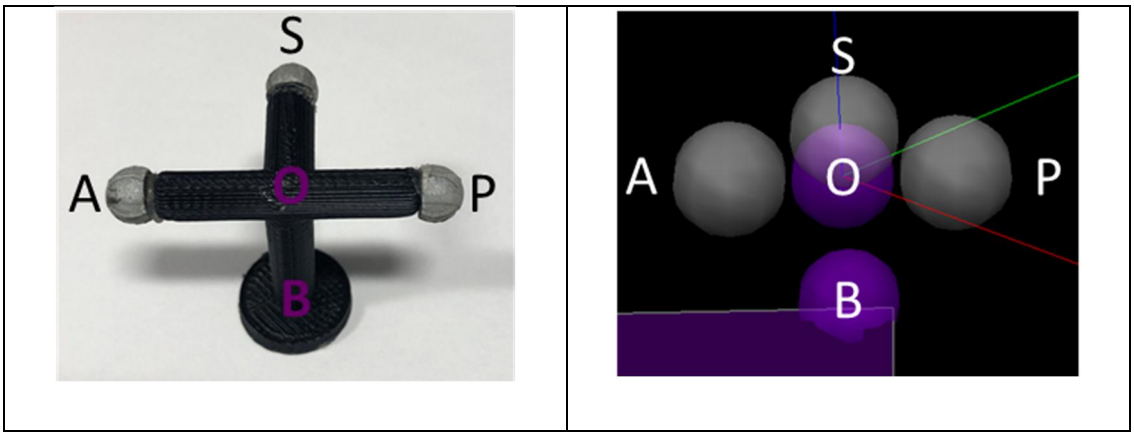


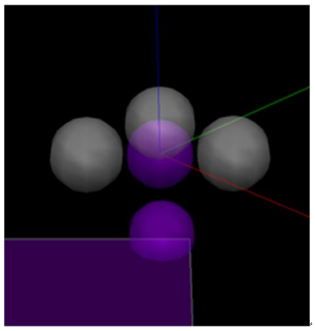
Figure 13a **Figure 13b**

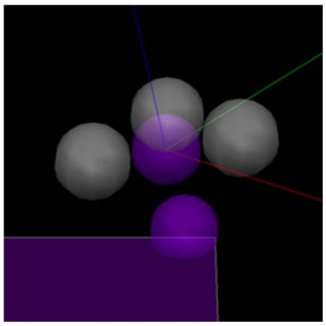
Figure 13: Cluster wand

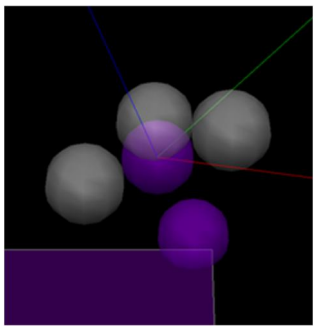
The marker used and landmark locations of the generated origin marker point and projected. **Figure 13b.** Generated virtual markers at origin (O) and base (B) in Visual 3d software (C-Motion, Germantown, USA). Anterior (A), superior (S) and posterior (P) = technical marker position on cluster wand (**Figure 13a**) and corresponding markers on in Visual 3D software (**Figure 13b)**

5.2.3.3 Results

When a bespoke cluster wand was positioned at zero, five and 10 degrees the base virtual mark maintained a position of 27mm about the origin marker (Figure 14). In addition, the displacement of the base marker maintained its coordinates of <0.007mm within the margin of error of the Vicon data collection system.







Zero degrees	Five degrees	Ten degrees
X:0.007002	**X**:0.007413	**X**: 0.004348
Y: 0.003032	**Y**: 0.002661	**Y**: 0.001870
Z: 0.003113	**Z**: 0.003770	**Z**: 0.004918

Figure 14: Cluster wand testing

Cluster wand orientation at gait laboratory base marker displacement from laboratory origin in the XY and Z

5.2.3.4 Conclusion

The findings from this pilot study indicate that the bespoke cluster wand is suitable for projecting a virtual marker for the collection of In-shoe kinematics. Findings justify the use of cluster wands to define the placement of the anatomical markers at the lateral calcaneus, first and fifth metatarsal heads and in turn, the generation of a virtual foot segment.

5.2.4 Pilot study part two: Boot and skin mounted kinematic comparison

5.2.4.1 Introduction

The collection of in-shoe kinematic and kinetic data can be problematic due to movement of the foot within the shoe and marker placement misrepresentation when placed on the shoe surface [127]. Shoe mounted markers have been used in the collection of kinematic data with a recent study using 3D printed wand markers reporting reliable data collection in-shoe [131]. The use of shoes with windows cut into mesh uppers to allow skin mounting of markers has also been reported, but in both instances, large portions of the shoe were removed and lacked the structural integrity of the military boot required as part of the LASER intervention [127, 131]. This second pilot study aimed to compare in-shoe ankle kinematics using foot-mounted cluster wands (actual) compared to markers mounted on the external surface of the boot, to determine whether the extra complexity of wand-based markers could be warranted and to finalise which method was to be employed in the LASER intervention study.

5.2.4.2 Method

Based on the rules of thumb for the recommended sample size for conducting pilot studies [300], 12 healthy participants were recruited from department staff. A 10 camera infrared passive marker motion capturing system operating at a frequency of 100Hz (Vicon MX, Oxford metrics, UK) was integrated with two force plates (AMTI, Watertown, MA) capturing force data at 1000Hz and arranged in succession allowing simultaneous collection of concurrent left and right side gait events. Lower limb kinematic data were collected using skin mounted nine millimetre (mm) reflective markers (Vicon MX, Oxford metrics, UK). Markers were placed following the CAST protocol marker set that tracks lower limb segment kinematics with six degrees of freedom [301]. Justifications for use of the CAST protocol have been presented in the Chapter Two literature review (Section

2.2.1.1.1: Lower limb models). Tracking marker clusters were placed on the sacrum, lateral thighs, and lateral shanks.

Figure 15: marker setup

a, Anterior view b, Posterior view

Gait data were collected for the left limb with both a shoe-mounted marker set and with in-shoe 3D printed cluster wands placed at the lateral calcaneus, 1st metatarsal phalangeal (MTP) joint and 5th MTP joint through 25 mm holes pictured in Figure 16 [126]. Each participant wore tight-fitting shorts to allow the fixation of reflective 9mm markers over anatomical landmarks to define joint centres at the hip, knee and ankle. Hip joint centres were calculated based on the embedded anatomical frame of the pelvis based on the recommendation of Bell *et al.* (1999) [302]. Reflective markers were placed on the left and right anterior superior iliac spine, and right and left posterior superior iliac spine. The knee joint centre was defined by marker placement at the condyles of the femur and the ankle medial and lateral malleolus [301].

Figure 16: Pilot Military boot with foot and boot-mounted marker sets

A static calibration was captured at the beginning of each footwear condition, a reference frame for the dynamic trials. If markers were lost or moved during a dynamic trial the marker or tracking pad was repositioned and another static trial was then collected for the subsequent trials. After an acclimatisation period of five minutes between footwear conditions, participants were instructed to walk, at a self-selected walking speed, up and down a 12-metre walkway. Measurement occurred within a $5m^3$ capture volume with gait events defined using two adjacent integrated AMTI force plates (Watertown, MA, USA). Each participant undertook a static reference trial followed by five representative walking trials. A trial was deemed acceptable if the participant made clean contact with either foot on the force plate during the participant's normal cadence. All static and dynamic trial markers were labelled and dynamic trials gap-filled using the spline fill function up to 10 frames using Vicon Nexus software 2.7.1(Vicon MX, Oxford metrics, UK). Labelled kinematic markers trajectories and kinetic data were exported to Visual 3D (C-Motion, Germantown, USA) for further analysis.

A biomechanical model was created using the methods described in the c-motion six degrees of freedom model that links segments of the pelvis, right and left thigh, right and left and right shank and left and right foot [303]. Linked segments were then used to calculate the kinematics and kinetics of the hip (pelvis and thigh), knee (thigh and shank) and ankle (shank and foot).

The biomechanical model was applied to the static trial with associated dynamic trials paired, based on the methods for building a six degrees of freedom model tutorial motion wiki (C-Motion, Germantown, USA) [303]. Kinematic data were interpolated to fill any gaps up to a maximum of 10 frames within Visual 3D (C-Motion, Germantown, USA) [304] and was filtered using a low pass Butterworth filter at a cut of frequency of below 6Hz. Ground reaction forces (GRF) were filtered using a low pass Butterworth filter at 25Hz with toe-on and toe-off above 20 N at heel strike and below 20 N for toe-off using thresholds from the GRF data [128, 305]. Calculations of ankle joint kinematics were derived using a single segment foot model with the proximal segment defined by the medial and lateral malleolus and the distal segment defined by the medial and lateral malleolar markers and foot markers used to track the segment. Ankle kinematics were calculated based on the C-motion 'foot model two' and calculated based on the knee markers (medial and lateral epicondyle) as the proximal segment and ankle, the distal segment (medial and lateral malleolus) tracked using the calcaneus, 1st metatarsal and 5th metatarsal markers. The use of foot model two calculates the ankle joint angle as zero in standing regardless to actual anatomical position [304]. This pragmatic approach was taken in preparation for use and comparison in a pathological cohort of patients with ankle haemarthropathy, where the foot is often affected by plantarflexion deformity and would not be captured faithfully using other methods [304, 306].

5.2.4.3 Analysis

Processed kinematic data was exported at 101 data points of the stance phase of gait for the ankle in the sagittal and frontal planes (X, Y) as mean values into a Microsoft excel 2018 worksheet. Specific time points of stance; initial contact (IC), midstance (MS) and toe-off (TO) were compared between conditions based on the anatomical points associated with the ankle rocker during the stance phase of gait and the theoretical concept that the LASER intervention will affect these points in the gait cycle [88].

Statistical analyses of the sagittal (X-axis) plane ROM at IC, MS and TO were undertaken to test for differences between conditions. ROM was calculated from the peak joint angles during the stance phase of gait for peak plantarflexion and peak dorsiflexion for ankle sagittal plane ROM and peak inversion and peak eversion. Ankle joint angles at IC, MS and TO were taken from 1%, 50% and 100% of the stance phase of gait. Statistical analysis of the sagittal plane kinematics (x-axis) was chosen for comparison between the LASER intervention, trainer and secondary outcomes due to its importance in the calculation of ankle kinetics and change in ROM observed in the sagittal, frontal and transverse planes [91]. Mean joint angles at IC, MS and TO were compared between conditions in the Y (coronal plane) and Z-axis (transverse plane) of the ankle joint. To assess the reliability of the foot-mounted (FM) and boot-mounted (BM) datasets intraclass correlations (ICC) were calculated using two way, mixed effect consistency, single rater (ICC 3,1) ICCs to report agreement between marker sets [307]. Root mean square error (RMSE) and a paired 2 tailed t-test was undertaken to assess error between measurements and explore for systematic differences in mean ROM in the sagittal plane (x-axis), respectively. Statistical analysis was carried out using IBM Statistical Package for Social Sciences (SPSS) version 21.

5.2.4.4 Results

Descriptive ankle joint kinematics in the sagittal, frontal and transverse planes are presented in Table 18. The largest variation between marker set measurements occurred in the frontal plane at IC, sagittal plane in MS and TO. In sagittal plane gait events, the boot-mounted marker set over-reported ankle joint angles when compared to the in-shoe foot model kinematics. In the frontal plane, the boot-mounted marker set over reported at TO and under-reported transverse plane kinematics at IC and TO.

Table 18: **Ankle joint kinematics (degrees)**

Plane	**Sagittal (X)**		**Frontal (Y)**		**Transverse (Z)**	
Footwear Condition	**FM**	**BM**	**FM**	**BM**	**FM**	**BM**
IC						
Mean	-1.30	-1.59	1.58	3.67	1.87	1.73
SD	1.65	2.18	1.27	3.39	2.29	2.38
Minimum	-4.18	-5.45	0.02	-2.20	-3.00	-2.73
Maximum	1.41	2.72	3.92	10.22	4.77	4.49
MS						
Mean	2.39	4.29	-3.90	-3.41	-0.31	-0.40
SD	1.14	1.17	1.22	1.75	3.02	2.91
Minimum	0.57	2.55	-6.32	-6.28	-7.13	-7.33
Maximum	4.93	7.13	-2.27	-0.82	5.15	5.49
TO						
Mean	-7.78	-10.57	1.93	3.23	5.37	5.72
SD	2.21	2.98	2.18	3.54	4.89	4.67
Minimum	-11.03	-16.49	-0.96	-1.36	-1.71	-1.37
Maximum	-2.69	-3.71	5.94	10.70	14.06	13.30

FM= foot markers, BM= boot markers, SD= standard deviation. Stance phase gait events; IC= initial contact, MS= midstance, TO= toe-off.

Mean sagittal plane ankle kinematic profiles are presented in Figure 17, with the boot condition demonstrating greater magnitudes of dorsiflexion at MS, and increased plantarflexion at TO. Ankle inversion/eversion in the frontal plane Figure 18 shows the boot-mounted markers larger variation in measurement at IC, but little difference was reported in foot angles between conditions.

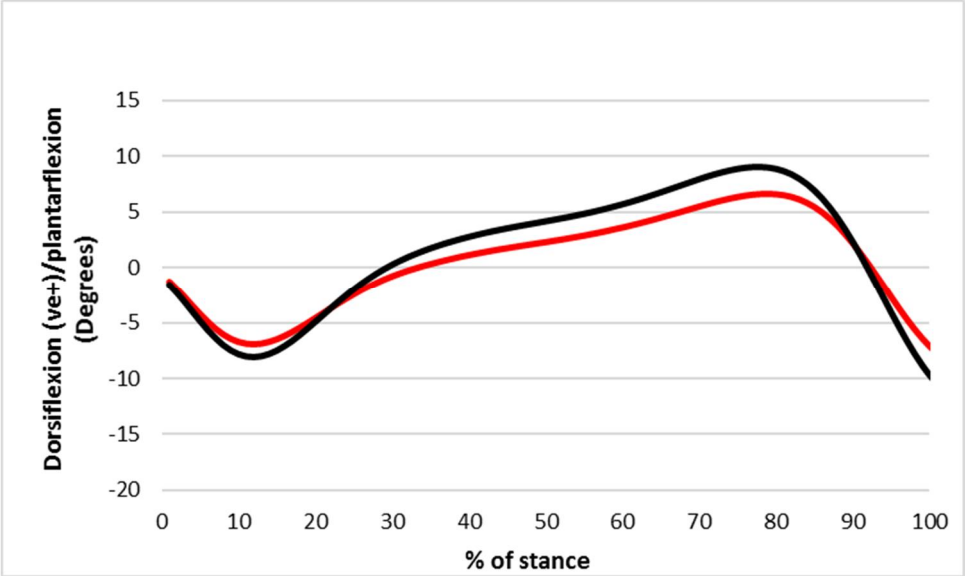


Figure 17: Mean ankle kinematics in the sagittal plane

A red kinematic profile represents foot mounted marker set; a black kinematic profile represents a boot-mounted marker set. Stance phase gait events; 0%= initial contact (IC), 50%= midstance (MS), 100%= toe-off (TO)

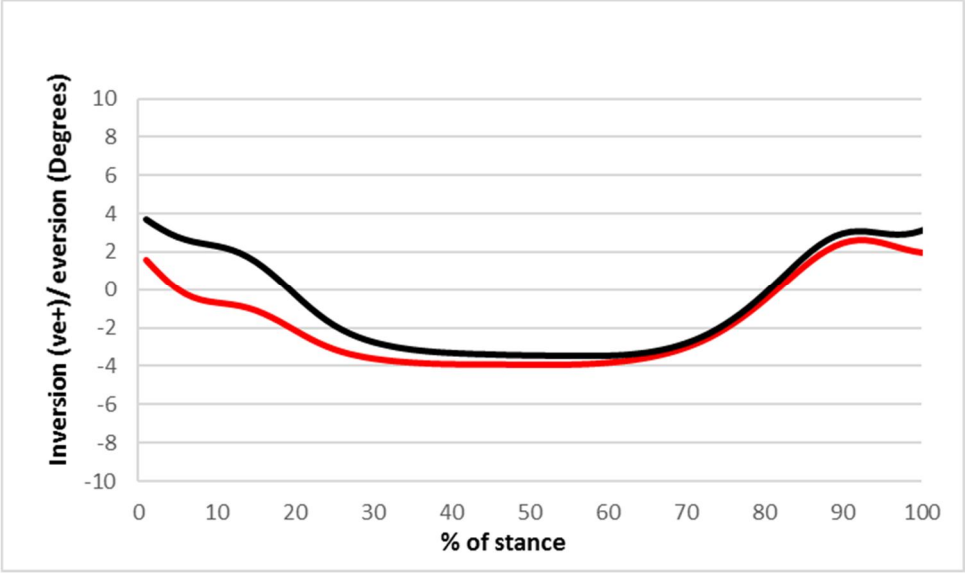


Figure 18: **Mean ankle kinematics in the frontal plane**

Red = foot mounted marker set, black = boot-mounted marker set. Stance phase gait events; 0%= initial contact (IC), 50%= midstance (MS), 100%= toe-off (TO)

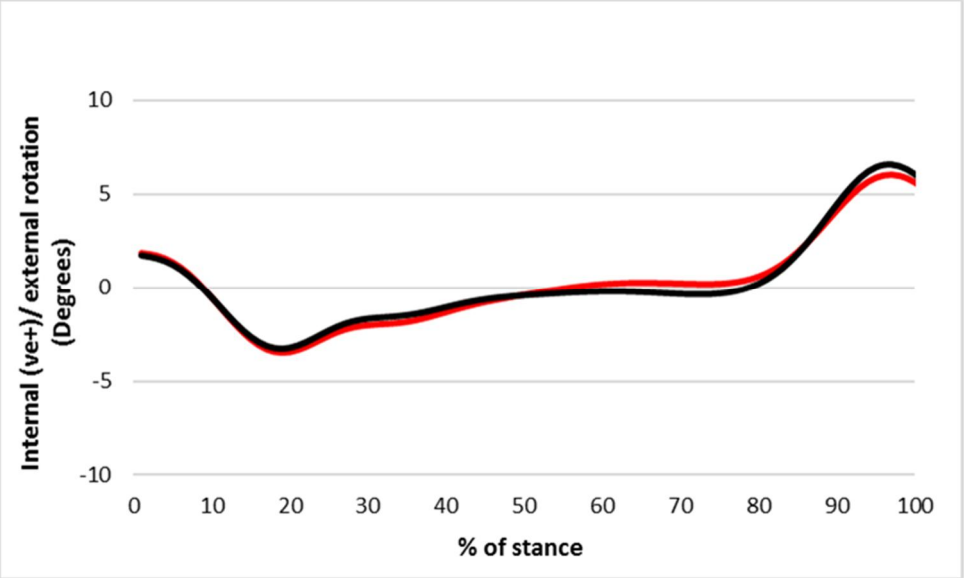


Figure 19: **Mean ankle-foot progression ankle in the transverse plane**

Red = foot mounted marker set, black = boot-mounted marker set. Stance phase gait events; 0% =initial contact, 50% = midstance, 100%= toe-off

ICC of sagittal plane ankle joint angles between FM and BM at IC, MS and TO are presented in Table 19. ICC at IC (.961), MS (.979) and TO (.981) report excellent correlation.

Table 19: Intraclass Correlation Coefficients of sagittal plane kinematics during the stance phase of gait			
	Intraclass Correlation	95% Confidence Interval	
		Lower Bound	Upper Bound
IC			
Single Measures	.925[a]	.761	.978
Average Measures	.961[c]	.864	.989
MS			
Single Measures	.959[a]	.864	.988
Average Measures	.979[c]	.927	.994
TO			
Single Measures	.849[a]	.558	.954
Average Measures	.918[c]	.716	.976

Stance phase gait events; IC= initial contact, MS= midstance, TO= toe-off.

RSME are presented in Table 20**.** The greatest RSME was reported at IC 1.01 degrees with MS at 0.71 and TO 0.29.

Table 20: **Root mean square error (RMSE) of sagittal plane kinematic gait events during the stance phase of gait**			
Gait events	**Mean absolute deviation (MAD)**	**Mean square error (MSE)**	**Root mean square error (RMSE)**
IC	0.66	1.02	1.01
MS	1.90	0.51	0.71
TO	5.31	0.08	0.29

Paired t tests were performed (Table 21) to compare the mean values between maker sets. A significant increase in mean difference was reported in the boot marker set with increased ROM reported in the sagittal plane at MS (p<.0001) and TO (p<.0001).

Table 21: T test of sagittal plane kinematic gait events during the stance phase of gait							
Gait event	Mean	SD	SE	**95% Confidence Intervals**		**t**	**Sig (2 tailed)**
				Lower	**Upper**		
IC	0.29	0.78	0.23	-0.21	0.79	1.28	0.23
MS	-1.90	0.35	0.10	-2.12	-1.68	-19.03	0.00
TO	2.79	1.51	0.43	1.83	3.75	6.42	0.00

SD= standard deviation, SE= standard error

5.2.4.5 Conclusion

A pilot study was undertaken to determine the appropriateness of shoe-mounted marker placement versus an in-shoe marker set generated by cluster wands placed on the foot to calculate ankle joint kinematics during normal walking. Results indicate that the BM set over-report ankle kinematics research that shoe-mounted marker sets that report significant discrepancies in ankle kinematics using shoe-mounted marker sets [124, 125]. The finding of this study is contrary to previously cite research that boot-mounted marker sets under-report kinematics, as the boot marker set in this pilot study over reported kinematics in the sagittal at all stance phase gait events, MS in the transverse plane and all three planes (X, Y, Z) at TO.

An explanation for our finds can be found in several reasons. Previously cited research has used inferior lower limb biomechanical modelling to obtain kinematic data which are known to incorporate error in the measurement of ankle kinematics (see section 2.2.1.1.1). The use of a military boot in this study is significantly more rigid than the trainers cited in other marker set comparisons the rigid structure may therefore not of been subjected to the same levels of movement artefact on the shoe. Graphical profiles (Figure 17-19) were similar between conditions, with ICC and RMSE showing high agreement between marker sets. Therefore it could be suggested the use of the boot marker set would be an acceptable method of data capture and significantly easier to undertake. However, the significant differences in sagittal plane kinematics at MS and TO may lead to the over estimation of sagittal plane kinematics, potentially resulting in significant levels of error in the proposed main study (Section 5.3). In addition to the primary finding of the study, the cluster wand successfully collected foot mounted kinematics without fouling the cluster wands during dynamic trials. The foot segment was generated by three marker clusters and therefore used only three 25mm holes which minimised the loss of shoe integrity. Therefore the methods presented in this pilot study represent a robust “gold standard” approach to the investigation of ankle kinematics and footwear evaluation.

5.3 The effect of the LASER intervention on the kinetic and kinematic profile of the lower limb

5.3.1 Background

The LASER intervention, a combination of the LASER boot and an FFO is used clinically in the management of ankle haemarthropathy at the Leeds haemophilia comprehensive care centre (CCC). Historical audit data for Leeds CCC indicates that footwear and FFO, including the LASER intervention, reduce bleeding foot and ankle pain and function [15]. However, only a small number of studies have investigated the use of footwear and FFO or other modified footwear interventions in ankle haemarthropathy [188, 308]. The use of FFO has been investigated in patients with haemophilia, but low-level evidence is quasi-experimental, and non-randomised studies limit reported benefits that FFOs reduced pain and disability. The reduction of episodes of bleeding and additional clotting factor concentrate (CFC) are similarly reported, but to date, no definitive trial has been undertaken [175, 294]. Footwear worn by patients with ankle haemarthropathy can have a significant effect on forces acting on the ankle joint [188]. The mechanism by which the LASER intervention alters lower limb kinetics and kinematics remain unclear despite positive clinical observations [15]. Therefore before undertaking a biomechanical study in the haemophilia population, who may be at risk when exposed to altered joint forces, investigating the effect of the LASER intervention on the ankle and lower limb kinetics and kinematics of healthy adult males is appropriate. Investigating the individual and combined components of the LASER intervention will establish the mechanism of action, and allow refinement of the design prior to future testing in a pathological haemophilia cohort and a future RCT.

It is hypothesised that the LASER intervention will reduce the mechanical demand on the ankle joint moment of force (Nm.kg) in the sagittal and frontal planes. The modification of a double rocker sole and SACH on a military boot in combination with an

FFO (LASER intervention) will substitute for the movement normally required of the ankle during walking.

5.3.2 Participants and methods

5.3.2.1 Aims and Objectives

This study aimed to investigate the mechanism of action of the LASER intervention using 3D gait analysis to understand the effect of the LASER boot modifications and FFO on kinetics and kinematics of the ankle and proximal joints of the lower limb.

Analysis in biomechanical studies have historically received criticism for the use of small sample sizes and the use of multiple statistical tests of dependant variables from the same dataset, which increase the risk of type I error [309, 310]. To prevent this in the current study predetermined and limited set of the most likely clinically and functionally meaningful variables were defined before testing of the LASER intervention. To test the mechanical effect of each footwear condition, outcomes were agreed by RAW and research supervisors (AR, GC) based on the proposed mechanical effect of each footwear condition as described in section 5.3.5.3. Primary, secondary and experimental biomechanical outcomes were produced to obtain unbiased condition effects and improve the validity of the data reported [309].

5.3.2.1.1 Primary objective

To determine the effect of the LASER interventions individual and the combined effect on internal ankle plantar/dorsiflexion and inversion/eversion moments of force (Nm.kg) when compared to a standard training shoe acting as a control shod condition.

5.3.2.1.2 Secondary objectives

To compare the individual and combined components of the LASER intervention on lower limb kinetics and kinematics. Specific secondary objectives are as follows:

- The kinematic effect on the ankle in the sagittal and frontal planes.
- The kinetic effect on the knee and hip in the sagittal and frontal planes.

- Observation of vertical, anterior/posterior and medial/lateral (Z, X, Y) ground reaction forces (GRF).
- Temporal and spatial parameters differences of walking speed, cadence, step length and double support.

5.3.2.1.3 Exploratory objectives

To investigate the mechanical effect of individual components of the LASER intervention compared to a standard training shoe.

5.3.2.1.4 Footwear condition-specific conditions

Comparisons will be based on the individual footwear modifications incorporated into the LASER boot (described in methods) and their proposed mechanical effect, providing clinical context to results. A pre-defined set of measures were selected to compare the effect of LASER intervention modifications to a standard trainer.

The following comparisons will be undertaken:

- The effect of the military boot on ROM at the ankle joint.
- The effect of a military boot with a SACH on peak plantarflexion ROM.
- The effect of a military boot with a rearfoot and forefoot rocker on the progression of GRF centre of foot progression (CoP).
- The effect of the LASER boot with and without an FFO on the kinetics and kinematics of the ankle joint.

5.3.3 Primary Hypothesis

A combination of the LASER boot and FFO will reduce the mechanical demand on the ankle joint by reducing the moment of force (Nm.kg) when compared to a standard trainer.

5.3.4 Methods

5.3.5 Ethical review

In accordance with the Declaration of Helsinki, seventh revision [311] local ethical approval was obtained from the University of Leeds, School of Medicine Research Ethics committee (MREC16-087).

5.3.5.1 Study Design

A single-centre, six-period, six-treatment, Williams Latin-Square cross-over design (within-participant comparison) was used to investigate the individual and combined components of the LASER intervention. The Williams design is suitable where there are more than two treatments/ conditions in a trial, and is a type of Latin square [312, 313]. Unlike a traditional Latin square, the Williams design is balanced for the carryover effect. Therefore the participant receives the same interventions in a randomised order. Participants were randomised to a sequence of interventions and control in a 6-period Williams Latin Square design [54, 55]. A 6 by 6 Williams Latin square was generated (Table 22) where each condition is represented once only per sequence. The table was repeated six times to generate the total participant number and balance the number of sequences that were randomised to each participant.

Table 22: Williams Latin square six by six sequence

Participant	**ORDER OF CONDITION**					
1	*A*	*B*	*C*	*D*	*E*	*F*
2	*B*	*D*	*A*	*F*	*C*	*E*
3	*C*	*A*	*E*	*B*	*F*	*D*
4	*D*	*F*	*B*	*E*	*A*	*C*
5	*E*	*C*	*F*	*A*	*D*	*B*
6	*F*	*E*	*D*	*C*	*B*	*A*

Individual sequences were randomly allocated by study number (0-36) to a sealed brown envelope by a research officer (LC). To avoid allocation bias the research officer randomised the sequences using an online random sequence generator (random.org). A record of the randomisation was then recorded on a database by the research officer to allow an audit of the sequence throughout the study. On the day of data collection, the research officer then allocated an envelope containing the sequence in ascending order at the point of data collection and participant consent.

5.3.5.2 Participants

Thirty-six healthy adult male participants were recruited from the University of Leeds Alumni group and the University of Leeds staff. All participants had no history of lower limb surgery or co-morbidities associated with foot and ankle pathology such as diabetes and inflammatory arthritis. Healthy participants were recruited to observe the biomechanical effects of footwear conditions in the absence of pathology. Inclusion exclusion criteria are presented in Table 23.

Table 23: Inclusion/ exclusion criteria

Inclusion criteria	Exclusion criteria
• Male • Aged 16 to • Free from musculoskeletal and neurological disease • Able to give informed written consent • A normal foot posture (defined as a Foot Posture Index score between +1 to +6) • Ability to walk unaided • The ability to read and understand English	• Under 16 years of age • Females (only 1 in 25million females are affected by haemophilia) • A history of below-knee surgery and significant comorbidities where changes to the mechanical function of the ankle joint alter the biomechanics of the foot • Extremes of foot posture (FPI-6 more than +8 (low arched) and below 0 (high arched)

Before enrolment, potential participants were screened for a “normal” foot posture defined by the foot posture index 6 (FPI-6) with normal defined as neither supinated nor pronated [314]. If the participant's foot posture was deemed normal (FPI-6 score of 1-6) and they had no other comorbidities that may affect gait then they consented following good clinical practice guidelines [315]. The participant was asked to identify their dominant foot (left/ right) thereafter known as the study limb, and footwear size. Participants enrolled in the study attended a one-time visit to the Chapel Allerton Hospital gait laboratory (University of Leeds, Leeds Teaching Hospitals NHS Trust) for data collection.

5.3.5.3 Footwear conditions

The six footwear conditions are summarised in Table 24 with descriptions provided in section 5.3.5.3.1. All adaptions were undertaken by a single technician by Steeper's group (Steeper Inc, Leeds, UK).

Table 24: Footwear experimental conditions

A: Standard trainer, no adaptation	**B:** Military boot, No adaptation	**C:** Military boot with SACH
		
D: Military boot with rearfoot and forefoot rocker sole	**E**: LASER boot	**F:** LASER boot with FFO
		 

SACH= Solid ankle cushion heel, FFO = functional foot orthoses. Holes in boot depict data collection windows for cluster wand placement.

5.3.5.3.1 LASER boot design

The LASER boot was developed and used in clinical practice by Lee Short, Extended Scope Practitioner podiatrist at the Leeds CCC. The design was later standardised by Richard Wilkins. The design of the LASER boot came about due to an unmet clinical need for the management of ankle haemarthropathy, poor compliance with footwear supplied by orthotic services and a more functional approach to the management of ankle joint kinetics and kinematics as opposed to the accommodation of structural deformity. The LASER boot (Figure 20) is designed to reduce the mechanical demand on the ankle joint in the presence of haemarthrosis and haemarthropathy in patients with haemophilia and other bleeding disorders associated with blood induced ankle arthritis such as type III Von Willebrand's diseases. The LASER boot comprises different components that are commonly used in footwear adaptations consisting of a 'heel-toe rocker sole, modified SACH heel and military-style boot.

Figure 20 Leeds Ankle Stabilising Enhanced Rocker (LASER) boot

A= rearfoot rocker, B= SACH heel, C= 8mm EVA, D= forefoot rocker position (60% of boot)

5.3.5.3.2 Military boot (Condition B)

The military-style boots, SWAT 8” force side zip boot (Original S.W.A.T, Morristown, TN) were used for adaptation. The military-style boot is designed to provide a solid base of support and provide a platform for adaptation. The upper shaft of the boot in combination with lacing and side zip fastening provide fixation around the ankle joint and lower shank. In the military where a multitude of terrain provides a challenge to preserving a level of adaptation whilst preventing injury such as ankle sprain by providing a level of fixation at the ankle joint [316].

5.3.5.3.3 Rocker sole (Condition C)

The rocker sole consists of a rearfoot (Figure 20a) and forefoot rocker (Figure 20d) manufactured by the addition of an 8mm high-density Ethylene-vinyl acetate (EVA) full length raise to a military boot. The EVA is then grinded down (Figure 20c) to accommodate the rocker profile adaptation. The rocker profile allows forward progression of the body’s centre of mass over the foot during the stance phase of the gait cycle [187]. The forefoot rocker is positioned at 60% of the shoe (Figure 20d) and is reported to be the optimal position in the management of forefoot pressures and facilitate movement where ankle ROM is limited [188].

5.3.5.3.4 SACH heel (Condition D)

Traditional SACH heels are used in prosthetics using a soft material that deforms under load. The SACH is made up of nora® Lunalastik (nora® SYSTEMS, GMBH) material with a shore rating of A25, specifically designed for use in the manufacturing of footwear. A Shore rating of A25 was chosen to allow gradual deformation under load whilst maintaining a level of stability as the rearfoot is loaded up to the midstance of gait. The traditional length of the SACH heel is around 1cm but is extended to 2cm to control the acceptance of load and decrease the risk of instability [194].

5.3.5.3.5 Functional foot orthoses

An X-Line standard (Healthystep, Manchester, UK) FFO without adaptation was used to assess the effect of the FFO in combination with the LASER boot (condition F). Changes in foot pressure and foot deformity are associated with ankle haemarthropathy in haemophilia [176]. The X-Line standard consists of a heel cradle and midfoot contoured support, metatarsal support and a 1st MTP joint depression providing rearfoot control, and midfoot support to stabilise the foot then loaded. The x-line standard is currently used clinically in haemophilia at the Leeds CCC. Nationwide, x-line FFOs are used in FFO trials and is the most widely used FFO in the NHS [317-319].

5.3.5.3.6 Trainer (condition A)

A standard trainer, the ASICS patriot 8 (ASICS Oceania Pty Ltd, USA) consists of a single EVA sole unit and laced upper. A trainer was chosen for comparison as the type of footwear recommended in clinical practice and did not contain any additional mechanical effect such as a medial or laterally posted rearfoot seen in other running footwear.

5.3.5.3.7 Outcomes

A predefined set of outcomes were chosen before data collection, based on the proposed mechanism of action of the LASER intervention (condition F) compared to a standard trainer (condition A). Secondary biomechanical outcomes were chosen to analyse the effect on ankle ROM and explore the biomechanical effects of the intervention on the knee and hip.

Primary outcome; LASER boot plus orthoses vs trainer

- Peak plantarflexion/dorsiflexion moment (Nm.kg) in the sagittal (X) and frontal (Y) plane as a measure of mechanical demand at the ankle joint.

Secondary outcomes; LASER boot and FFO vs trainer

- Peak knee and hip moments in the sagittal and frontal planes
- Total ROM, maximum plantarflexion and dorsiflexion at the ankle joint

- Total ROM, maximum flexion and extension at the knee and hip
- Maximum and minimum GRF X/Y/Z (observational)
- Temporal and spatial parameters: walking speed, cadence, step length, double support

Exploratory

Footwear condition-specific vs a trainer (condition A)

- Military boot: sagittal and frontal plane ankle joint ROM (condition B)
- SACH heel: ankle joint peak plantarflexion moment (condition C)
- Rocker sole: GRF centre of progression width and length (condition D)
- LASER boot only: as per primary comparisons (condition E)
- FFO effect: Laser boot only vs LASER intervention (condition E, F)

5.3.5.4 Data collection

As described previously, a 10 camera infrared passive marker motion capturing system operating at a frequency of 100Hz (Vicon MX, Oxford metrics, UK) integrated with two force plates (AMTI, Watertown, MA) capturing kinetic data at 1000Hz and arrange in succession allowed simultaneous collection of concurrent gait events. Lower limb kinetic and kinematic data were collected using skin mounted nine millimetre (mm) reflective markers (Vicon MX, Oxford metrics, UK). Markers were placed in accordance with the CAST model details of which are provided in section 5.2.4.2 [301]. Study limb in-footwear gait data were collected using 3D printed clusters wands placed at the lateral calcaneus, 1st MTP joint and 5th MTP joint through 25 mm holes pictured in Figure 21 [126]. Additionally, markers were placed on the proximal joints and segments. The cluster wands were used to define the study limb foot. The contralateral “non-dominant” foot was defined with footwear mounted markers at the 1st, 2nd and 5th MTP joints and the posterior calcaneus using the same skin mounted 9mm reflective lower limb markers. Following the collection of data for each footwear condition (A-F) ankle and foot markers were removed to allow for footwear change and were reapplied once the footwear was

secured. Proximal markers and tracking pads were repositioned carefully by an experienced MSK podiatrist (RAW) to ensure correct anatomical position and maximise the accuracy of the data.

Figure 21: Cluster wand placement

Right foot cluster wand placement on the A, lateral calcaneus, B, 5th metatarsal head and C, 1st metatarsal head. Left foot corresponding boot-mounted marker set.

5.3.6 Data Capture and processing

36 participants undertook gait analysis using the methods described in section 5.2.4.2. Participants were asked to place the boot on each foot and lace-up using all eyelets to the top of the boot. Once the boot was laced, participants were asked to fasten the side zip of the boot so the boot felt “secure, but not uncomfortable”. Details of the processing of static and dynamic trials are provided in section 5.2.4.2. Data was exported to excel 2018 as the mean minimum and maximum kinetics and kinematics of the five representative gait trials of each condition and each footwear condition (A to F).

5.3.7 Sample size

A sample size of 36 participants provided 80% power to detect a standardised effect size of 0.5, assuming a 2-sided 5% significance level. Equal numbers of participants were allocated to each sequence to ensure balance. Wang *et al.* (2009) describe that the

number of participants needed to power the trial is a multiple of the condition times by itself. Replicating the design six times required 36 participants [313].

5.3.8 Statistical analysis

Data were analysed graphically for each of the primary, secondary and exploratory outcomes by exporting data into Microsoft excel 2018 worksheet. Motion time curves were generated as mean for each individual segment (ankle, knee and hip) in the specified anatomical plane for the kinetic (X, Y) and kinematic (X, Y, Z) variable. Grand means were then exported for analysis. Descriptive statistics were produced using SPSS version 26 (Armonk, NY: IBM Corp). The mean, standard deviation (SD) and 95% confidence interval (95% CI) are presented for all primary, secondary and exploratory outcomes. To compare outcomes between conditions, a linear mixed model was fitted using Statistical Analysis Software SAS version 9.4 (North Carolina, USA: SAS Institute Inc.). Fixed effects were included for sequence, period, condition and prior condition, and random effects for participants within sequences, using PROC MIXED. Differences in the least-square means were extracted for conditions and prior conditions using LSMEAN. As the same participant acts as their own control, within-subject rather than between-subject differences were tested [320]. A two-sided significance level of 5% was used throughout, using type III tests of fixed effects. Overall effects are presented as statistic (F), degrees of freedom (DF) and significance (p-value). Treatment effects are reported as estimates, standard error, t value and significance (p-value). Estimation of parameters was undertaken using restricted maximum likelihood (REML). Finally, linear mixed model regression analysis was undertaken using the SAS Kenward-Roger method to model the relationship between exploratory conditions against the standard trainer in primary, secondary and exploratory outcomes [321].

5.4 Results

5.4.1 Participant characteristics

A total of 36 male participants consented to take part in the study with a mean age of participants of 31.1 years (SD, 7.9). Mean (SD) FPI-6 was 2.8 (SD 1.55) for the left foot and 2.89 (SD 1.35) for the right foot, which is within the normal foot posture range (neither supinated nor pronated). Participant mean weight of 82.2 kg (SD, 12.5) and height of 179cm (SD, 7) produced body mass index (BMI) measures of 25.5kg/m^2 (SD, 3.4).

5.4.2 Primary outcome

Ankle Kinetics

Comparison of ankle moment data between the LASER intervention and trainer is presented in Table 25. The LASER intervention reduced internal ankle plantarflexion, therefore reducing the rotational force at the ankle as the foot moves from the ankle to forefoot rocker, opposed to the plantarflexor musculature of the ankle. The internal plantarflexion moment was reduced by 0.18Nm.kg compared to the trainer which was statistically significant (P=<0.0001). Increase in peak internal dorsiflexion moment is caused by the LASER intervention as the heel makes contact with the floor (heel rocker) and is opposed by the dorsiflexor musculature of the ankle. The increase in internal dorsiflexion moment was small in magnitude (0.06Nm.kg), however significant (P=<0.0001).

Table 25: Ankle kinetic effect of the LASER intervention when compared to a trainer

Measure (Nm.kg) Mean (SD)	Trainer (A)	LASER intervention (F)	Condition A v F			
			Estimate	Standard error	T value	P-value
Peak ankle plantarflexion moment	1.55 (0.17)	1.37 (0.17)	0.179	0.0134	13.34	**<.0001**
Peak ankle dorsiflexion moment	-0.37(0.09)	-0.43 (0.08)	0.055	0.010	5.09	**<.0001**
Peak ankle inversion moment	0.15 (0.07)	0.15 (0.07)	-0.002	0.010	-0.26	0.798
Peak ankle eversion moment	-0.13 (0.07)	-0.12 (0.04)	-0.007	0.007	-0.99	0.322

A= trainer condition (control), F= LASER boot intervention. Significance level <0.05 (bold figures = significance)

Test of fixed effect

Type III tests of overall effects were undertaken to test the significance of sequence, period, condition, and prior condition (Table 26) on primary outcomes. The peak moment of ankle joint plantarflexion was significant for treatment only. Peak dorsiflexion was significant for treatment and period indicating some carryover effect of the previous intervention. Neither prior condition nor sequence was important, indicating no first-order carryover effects for any of the ankle joint kinetic parameters.

Table 26: Ankle kinetics type III tests of fixed effects

Measure (Nm.kg)	Effect	Num DF	Den DF	F value	P value
Ankle plantarflexion moment	Sequence	5	30	0.17	0.970
	Period	4	165	0.59	0.670
	Treatment	5	165	50.86	**<0.0001**
	Prior treatment	5	165	0.92	0.467
Ankle dorsiflexion moment	Sequence	5	30.2	0.65	0.662
	Period	4	165	2.51	**0.044**
	Treatment	5	165	28.08	**<0.0001**
	Prior treatment	5	165	1.62	0.156
Ankle inversion moment	Sequence	5	30.1	1.01	0.427
	Period	4	165	0.52	0.724
	Treatment	5	165	0.76	0.581
	Prior treatment	5	165	1.16	0.329
Ankle eversion moment	Sequence	5	30.4	0.68	0.638
	Period	4	165	0.93	0.447
	Treatment	5	165	1.61	0.159
	Prior treatment	5	165	1.55	0.178

Bold text= significance (p <= 0.05)

5.4.3 Secondary outcome measures

5.4.3.1 Ankle kinematics

Secondary comparisons of ankle kinematics are presented in Table 27. In the sagittal plane, the LASER intervention reduced total ROM by 4.6 degrees (P=<,0001). The largest change was in the reduction of peak plantarflexion (3.4 degrees, P=<0.0001), with a reduction of dorsiflexion of 1.6 degrees (P=0.0007). Peak inversion was reduced by 3.7 degrees for the LASER intervention, however, a small increase in peak eversion ROM (1.0 degrees) was observed. Both inversion and eversion peak ROM were significant.

Table 27: Comparison of ankle kinematics between the LASER intervention and trainer

Ankle ROM (degrees) Mean (SD)	Trainer (A)	LASER intervention (F)	Condition A v F			
			Estimate	Standard error	T value	P-value
Sagittal plane total plantarflexion/ dorsiflexion	26.3 (3.9)	21.7 (3.7)	4.5	0.3	15.2	**<.0001**
Sagittal plane peak plantarflexion	-17.8 (4.4)	-14.4 (3.3)	-3.2	0.4	-7.3	**<.0001**
Sagittal plane peak dorsiflexion	8.5 (3.7)	7.3 (3.1)	1.3	0.4	3.5	**0.0007**
Frontal plane Ankle total ROM	11.0 (2.1)	8.5 (1.8)	2.5	0.3	8.5	**<.0001**
Frontal plane peak inversion	11.1 (4.0)	7.4 (3.5)	1.2	0.3	3.8	**0.0002**
Frontal plane peak eversion	0.1 (3.5)	-1.1 (3.4)	3.6	0.4	9.5	**<.0001**

SD standard deviation

Comparison of total ROM at the ankle are present in Figure 22 and Figure 23. Ankle ROM in the sagittal plane (Figure 22) were 21.71° (SD, 3.77 95% CI: 20.44 to 22.99) and 26.31° (SD, 3.90 95% CI 24.99 to 27.63) in the LASER intervention and trainer respectively. Total ROM was reduced by the LASER intervention, with the most notable difference occurring towards the end of stance with a reduction in dorsiflexion and less plantarflexion at TO.

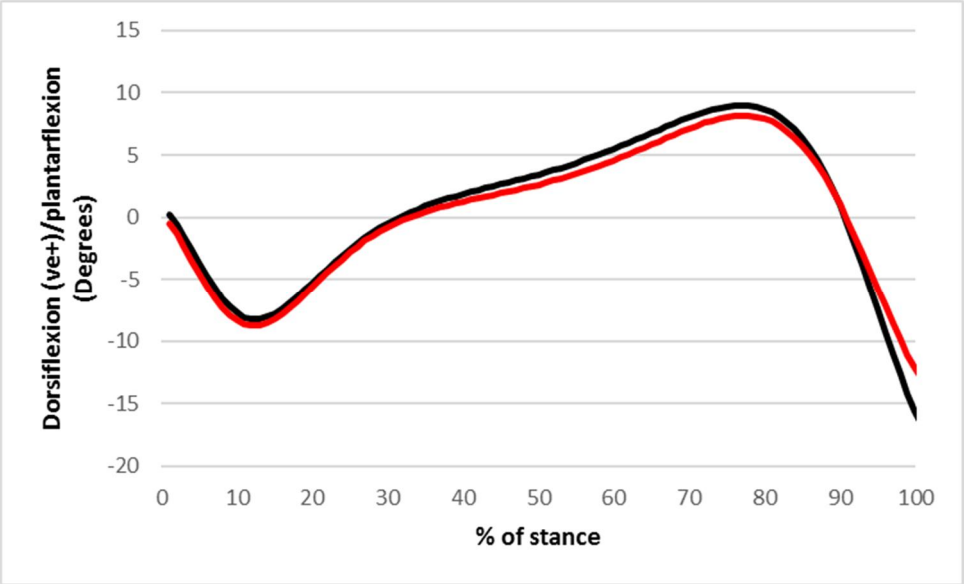


Figure 22: Ankle sagittal plane kinematics
The black line represents control A and Red line represents condition F (intervention)

Frontal plane ROM (**Figure 23**) yielded similar results with a mean reduction of total ROM in the LASER intervention of 8.5° (SD 1.84, 95% CI: 7.9, 9.2) compared to that of the trainer (mean 11.0° SD 2.1 95% CI: 10.3, 11.7).

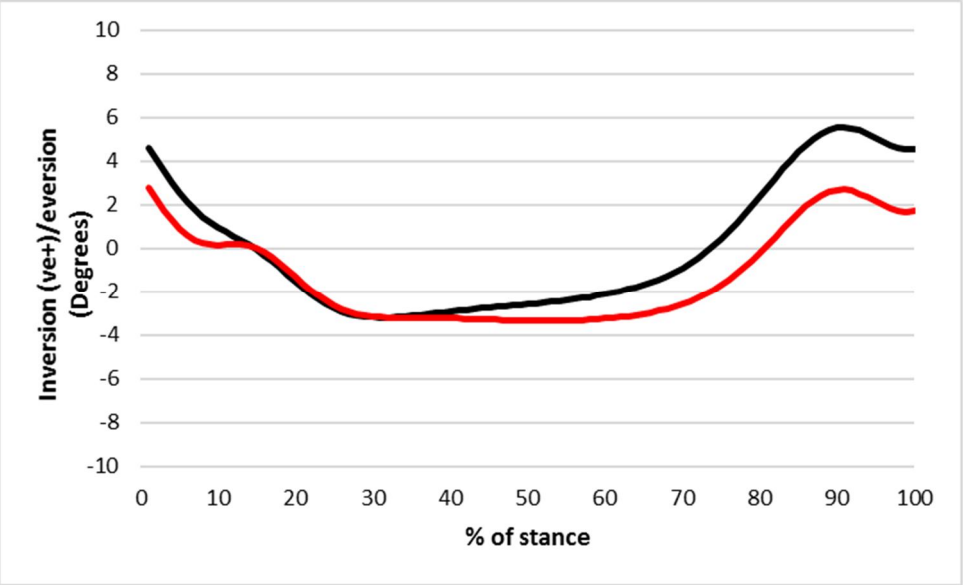


Figure 23: Ankle frontal plane kinematics
The black line indicated control A, Red line equals condition F (intervention)

Test of fixed effect

Test of fixed effect for ankle kinematics reported significance in treatment for all ankle kinematic outcome measures in the sagittal and frontal planes (P=<0.0001). Only peak ankle dorsiflexion and plantarflexion reported the significance of P=0.0032 (f value 3.7) and P=0.0211 (f value 2.7) respectively for prior treatment indicating a significant carryover effect in both parameters.

5.4.3.2 Knee and hip kinetics

Knee and hip kinetics are reported in Table 28. Knee extension moment in the LASER intervention (1.21 SD0.23 Nm.kg) vs trainer (1.16 SD0.29 Nm.kg) were not significant (P=0.0706). . Observations at the knee report an increase in knee adduction moment of -03 Nm.kg (P=<0.0001) at the hip both peak extension and adduction moments were also increased by 0.15 (P=<0.0001) and 0.03 Nm.kg respectively.

Table 28: LASER boot with a foot orthoses effect on Knee and hip kinetics when compared to a trainer

Moment (Nm.kg) Mean (SD)	Trainer (A)	LASER intervention (F)	Condition A v F			
			Estimate	Standard error	T value	P-value
Peak knee flexion moment	-0.37 (0.13)	-0.38 (0.14)	0.0132	0.013	0.98	0.328
Peak knee extension moment	1.16 (0.29)	1.21 (0.23)	-0.042	0.023	1.82	0.0706
Peak knee adduction moment	-0.08 (0.05)	-0.11 (0.06)	0.028	0.006	4.39	**<.0001**
Peak knee abduction moment	0.45 (0.14)	0.47 (0.15)	0.014	0.012	-1.20	0.2320
Peak hip flexion moment	-1.13 (0.19)	-1.14 (0.22)	0.010	0.022	0.47	0.6394
Peak hip extension moment	0.90 (0.23)	1.05 (0.28)	0.157	0.025	-6.14	**<.0001**
Peak hip adduction moment	-0.13 (0.08)	-0.16 (0.09)	0.029	0.010	2.88	**0.0045**
Peak hip abduction moment	1.12 (0.17)	1.14 (0.16)	-0.021	0.0166	-1.27	0.2049

5.4.3.3 Knee and hip kinematics

Knee and hip kinematic graphs over the stance phase of gait are presented in Figure 24. In the trainer condition, peak knee flexion was increased by a 3.2° (SD 3.9) and movement toward extension was decreased by 2.2° (SD 3.4) and remained in a more flexed position. Peak movement towards knee extension fall outside of the CI (LASER intervention, 49.8 to 52.4, Trainer 52.7 to 56.0) therefore representing a systematic difference. ROM at the hip was similar between conditions with only less than 0.3° between conditions in all parameters. Total knee and hip kinematics during the stance phase of gait are presented in Table 29.

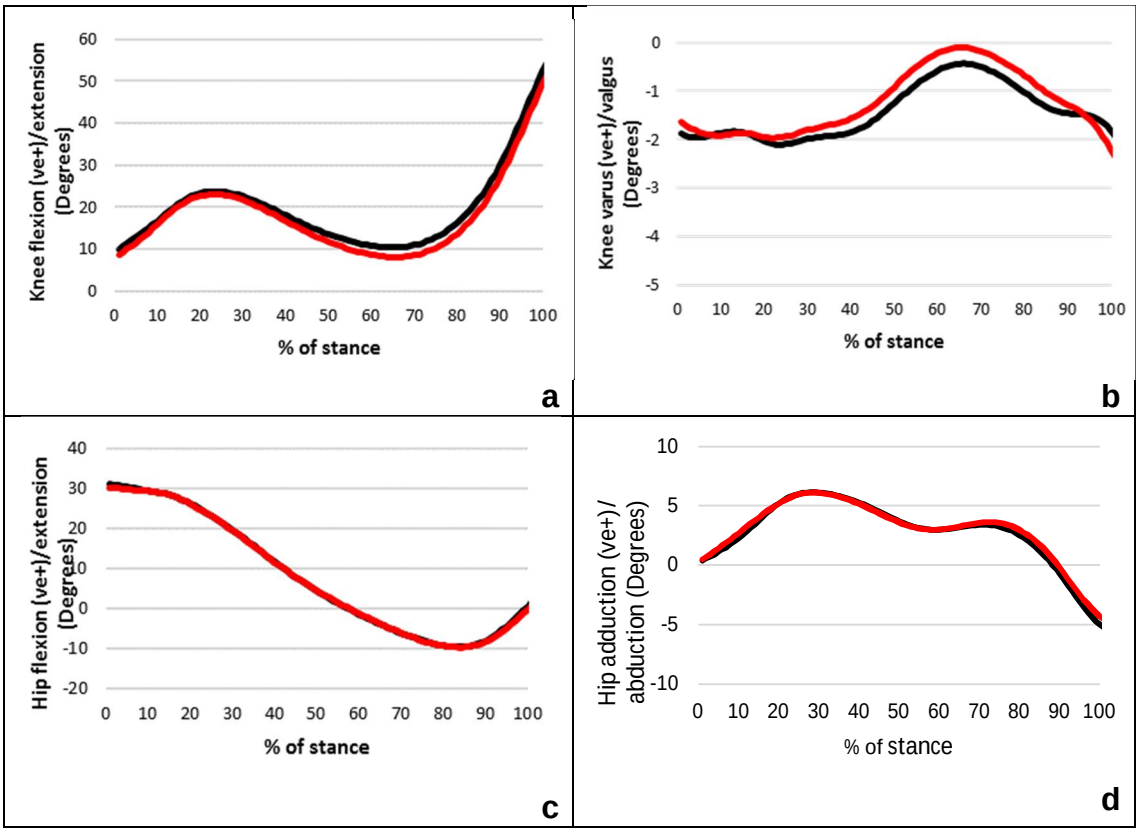


Figure 24: Knee and hip kinematics
Sagittal (a and c) and frontal plane (b and d) *Black line indicated control A, Red line equals condition F (intervention)*

Differences in the knee and hip kinematics are presented in Table 29. Sagittal plane ROM was significantly increased (P=<0.001) by mean 5.3° (SE, 0.3) in the LASER intervention compared to the trainer. Increases in ROM were attributed to significant increases in peak knee flexion (mean 3.3°), and peak knee extension (mean 1.9°, P=<0.0001, for both measures). Between-condition changes in frontal plane knee

kinematics were not found. Changes in total hip ROM were not significant in either the sagittal or frontal plane for the LASER intervention, therefore little proximal effect occurred at the hip during the stance phase of gait, indicating that the main effects occurred in the knee and ankle.

Table 29: LASER intervention effect on the knee and hip kinematics when compared to a trainer

ROM (degrees) Mean (SD)	Trainer (A)	LASER intervention (F)	Condition A v F			
			Estimate	Standard error	T value	P-value
Knee total ROM sagittal plane	45.1 (3.8)	44.5 (3.5)	0.7	0.4	2.2	**0.032**
Peak knee flexion	54.3 (4.8)	51.3 (3.9)	3.3	0.4	8.1	**<.0001**
Peak knee extension	8.6 (3.7)*	6.9 (3.1)	1.9	0.3	6.1	**<.0001**
Frontal plane knee total ROM	3.7 (1.9)	4.7 (2.5)	0.1	0.3	0.4	0.652
Peak knee adduction	1.1 (3.6)	1.2 (3.1)	0.01	0.3	0.3	0.767
Peak knee abduction	-3.9 (4.1)	-3.5 (4.1)	-0.3	0.3	-0.8	0.410
Hip total ROM sagittal plane	40.3 (5.4)	38.9 (5.2)	0.5	0.3	1.7	0.093
Peak hip flexion	31.7 (8.7)	31.3 (7.5)	0.5	0.7	0.6	0.544
Peak hip extension	-9.0 (7.9)	-9.2 (7.1)	0.3	0.7	0.4	0.689
Hip total ROM frontal plane	9.7 (2.5)	11.4 (2.6)	0.4	0.2	1.7	0.095
Peak hip adduction	6.5 (3.8)	6.4 (4.1)	0.1	0.4	0.3	0.7896
Peak hip abduction	-5.4 (3.2)	-5.1 (3.1)	-0.3	0.4	-0.8	0.453

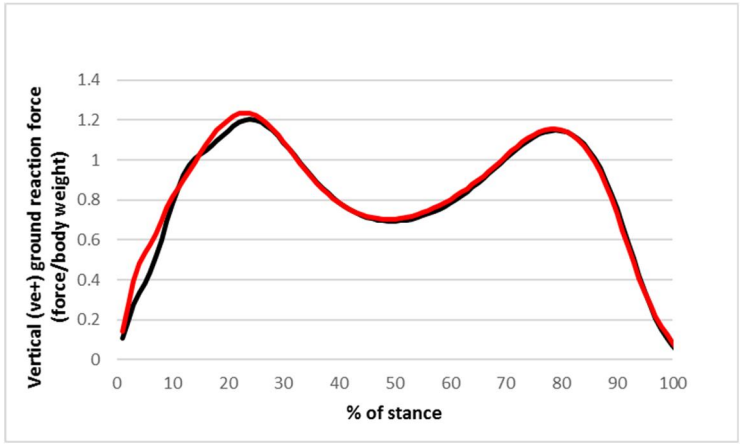
* Positive values indicate knee flexion

Tested of fixed effect

Secondary kinematic outcome measures tests of fixed effects were significant ($p<0.001$) for treatment for all knee outcome measures, indicating that treatment effects were independent of the period, sequence and prior treatment. Similarly at the hip, the treatment effect had a significant effect on total sagittal plane total ROM (P=<0.0001) and peak hip flexion (P=<0.01). In the frontal plane, there was a significant treatment effect for total hip ROM (P=<0.0001) and prior treatment (P=0.004) whilst there was a significant period effect for peak hip adduction (P=0.04).

5.4.3.4 Ground reaction forces

GRF graphs are presented in Figure 25**.** Few differences were apparent in anterior/posterior (Figure 25c) and vertical GRF (Figure 25a). Less variation in medial/lateral GRF (Figure 25b) was apparent up to 20% of stance where forces were similar between conditions.



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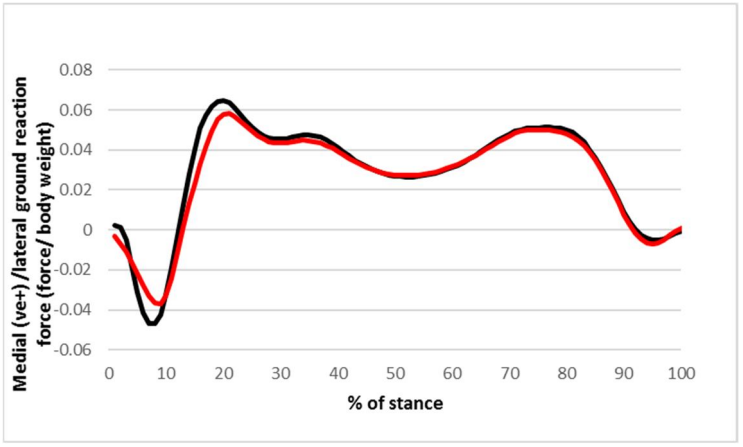

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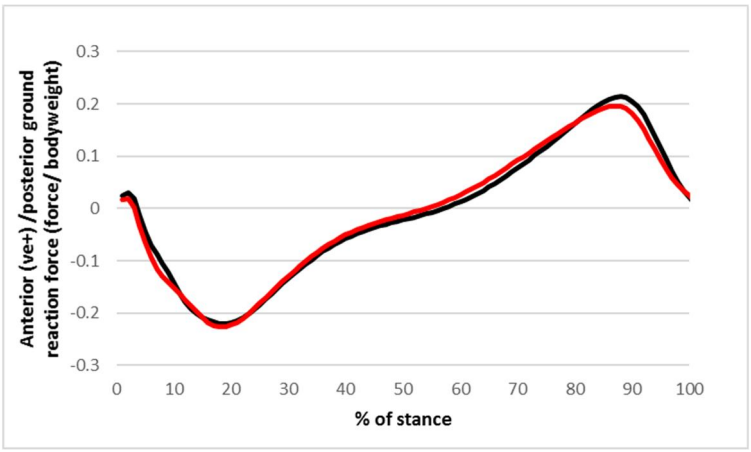


c

Figure 25: Ground reaction forces

The black line indicates control A, red line condition F (intervention)

Comparisons of the LASER intervention and trainer are presented in Table 30. Significant increases in minimum and maximum medial GRF and a decrease in posterior GRF were reported in the LASER intervention when compared to the trainer. Vertical GRF was also significantly increased.

Table 30: **Effect of LASER intervention on GRF compared to a trainer**

Force/body weight Mean (SD)	Trainer (A)	LASER intervention (F)	Condition A v F			
			Estimate	Standard error	T value	P value
Maximum vertical GRF	1.24 (0.09)	1.27 (0.08)	-0.030	0.008752	-3.44	**0.0007**
Maximum medial GRF	0.07 (0.02)	0.08 (0.02)	-0.006	0.002	-2.7	**0.007**
Minimum lateral GRF	-0.04 (0.02)	-0.05 (0.02)	0.013	0.002	5.93	**<.0001**
Maximum anterior GRF	0.22 (0.04)	0.20 (0.04)	0.017	0.002	6.35	**<.0001**
Minimum posterior GRF	-0.23 (0.04)	-0.24 (0.04)	0.006	0.004368	1.51	0.132

Test of fixed effect

Treatment had a significant fixed effect (P=<0.002) on all GRF outcomes in all planes (X, Y, Z) with the exception of minimum anterior/ posterior GRF that also reported significance in prior treatment (P=0.05). No fixed effect of sequence or prior treatment were reported in any of the GRF parameters.

5.4.4 Temporal and spatial parameters

Temporal and spatial parameters

Temporal and spatial parameters are a measure of overall function, therefore walking speed, cadence, step length and double support were compared between the LASER intervention and trainer. Descriptive analyses of temporal and spatial parameters are presented in Table 31. Walking speed, cadence and double support was significantly lower in the LASER intervention, but step length was unaffected.

Table 31: Changes in temporal and spatial parameters between the LASER intervention and a trainer

Parameter Mean (SD)	Trainer (A)	LASER intervention (F)	Condition A v F			
			Estimate	Standard error	T value	P value
Walking speed (meters/sec)	1.45 (0.13)	1.42 (0.13)	0.03	0.01	2.35	**0.0199**
Cadence (step/min)	111.12 (6.5)	108.96 (6.4)	2.16	0.61	3.55	**0.0005**
Step length (cm)	0.79 (0.06)	0.79 (0.05)	0	0	0.79	0.433
Double support (% of stance)	0.23 (0.05)	0.22 (0.05)	0.01	0	3.63	**0.0004**

Test of fixed effect

Test of fixed effected reported significance in temporal and spatial parameters for treatment only ($p<0.01$) in all temporal and spatial outcome measures. There were no significant effects of sequence of intervention, period and prior treatment on any temporal and spatial parameters.

5.4.5 Exploratory outcome measures

5.4.5.1 Descriptive statistics

To investigate the specific mechanical effect of the individual components of the LASER boot (conditions B, C, and D), each condition was compared individually to the control intervention (condition A). The effect of the LASER boot with (condition F) and without (condition E) FFO were compared to understand the effect of the FFO. Specific measures were chosen before analysis that represents the proposed clinical effect of each condition (discussed in section 5.3.2.1.4).

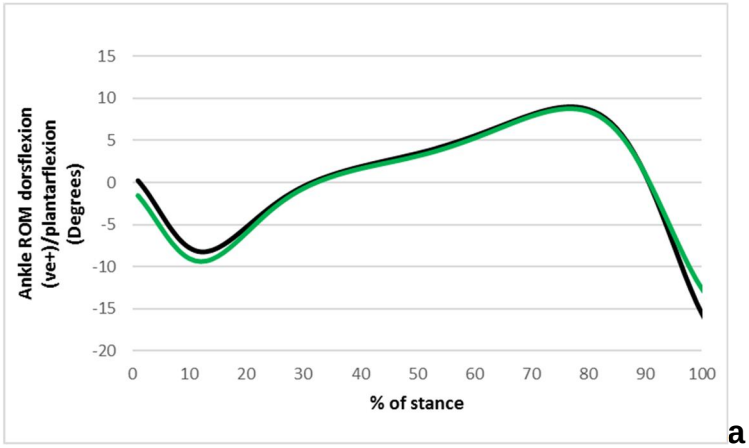
Test of fixed effect

The test of fixed effect was significant for all footwear conditions for treatment only (<0.001). Therefore no period, carryover or sequence effect was observed.

5.4.5.1.1 Footwear component effect

Military boot (Condition B)

Ankle ROM (X and Y) comparisons of the military boot and trainer are presented in Figure 26 as sagittal plane (Figure 26a) and frontal plane (Figure 26b) over the stance phase of gait. A systematic reduction in ankle ROM was reported in both the sagittal and frontal planes in the military boot. In the sagittal plane, the ROM (Figure 26a) were 26.3° (SD, 3.9 95% CI: 25.0, 27.6) for the trainer and 22.8° (SD, 3.3 95% CI: 21.7, 23.9) for the military boot. In the frontal plane (Figure 26b) the ROM of the trainer was 11.0° (SD 2.1, 95% CI: 10.3, 11.7) and for the military boot, 9.1° (SD, 1.9 95% CI: 8.5, 9.8). In both sagittal and frontal planes, CIs for the ROM in the boot lay outside of the boundary of the relevant Cis for the trainer. Statistical analysis (Table 32) indicates significance for these differences in both the sagittal and frontal planes, with total sagittal and frontal ROM reductions of 3.5° and 1.9° respectively.



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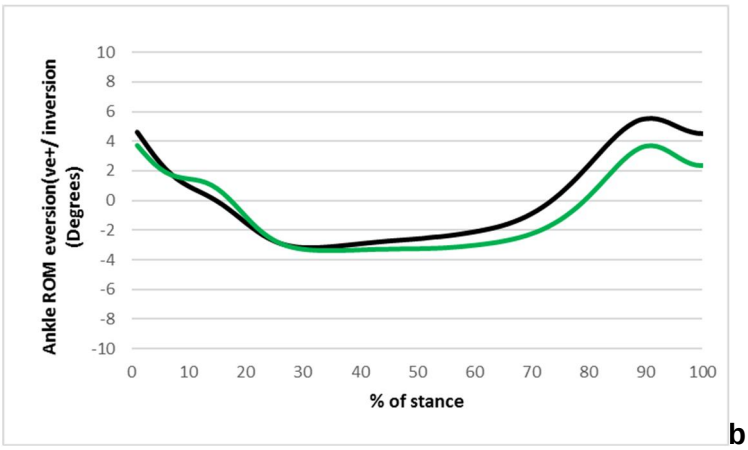

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Figure 26: Ankle range of motion of exploratory conditions

Black line = trainer, green line = military boot. Ankle ROM during the stance phase of gait. 5a, sagittal plane ROM (dorsiflexion/plantarflexion). 5b, frontal plane ROM eversion/inversion.

Table 32: Effect of a military boot on the total ROM at the ankle in the sagittal and frontal planes when compared to a trainer

ROM (degrees) Mean (SD)	Trainer (A)	Military boot (B)	Condition A v C			
			Estimate	Standard error	T value	P-value
Ankle total ROM sagittal plane	26.3 (3.9)	22.8 (3.3)	3.51	0.29	11.85	<.0001
Ankle total ROM frontal plane	11.0° (2.1)	9.1 (1.9)	1.92	0.29	6.63	<.0001

SACH heel modification (condition C)

Compared to a trainer, the SACH modification (Table 33**)** leads to a significant decrease in peak plantarflexion moment of 0.145 Nm.kg from 1.55 to 1.40 Nm.kg (P<0.0001).

Table 33: Effect of a SACH on peak plantarflexion moment (Nm.kg) when compared to a trainer

Moment (Nm.kg) Mean (SD)	Trainer (A)	SACH (C)	Condition A v C			
			Estimate	Standard error	T value	P value
Peak plantarflexion moment	1.55 (0.170)	1.40 (0.148)	0.145	0.013	10.8	**<.0001**

Forefoot and rearfoot "rocker bottom" sole (condition D)

Descriptive and inferential statistics for centre of pressure data presented in Table 34 revealed the rocker bottom sole reduced the minimum width of the GRF CoP progression by 0.011cm (P=<0.001), however maximum width was increased by 0.010cm (P=<0.0001). GRF CoP maximum length was increased by 0.001cm, and whilst very small in change was significant (P=0.01) indicating the rocker soled shoe increased the surface in contact with the floor when compared to the trainer.

Table 34: Exploration of the rocker sole effect on GRF centre of pressure trajectory when compared to a standard trainer						
CoP cm Mean (SD)	**Trainer (A)**	**Rocker sole boot (D)**	**Condition A v D**			
			Estimate	**Standard error**	**T value**	**P value**
Rocker sole GRF centre of progression: min x (width)	0.031 (0.03)	0.020 (0.033)	0.009	0.002	3.34	**0.001**
Rocker sole GRF centre of progression: max x (width)	0.069 (0.03)	0.079 (0.029)	-0.010	0.002	-4.75	**<.0001**
Rocker sole GRF centre of progression: Y length min	-0.059 (0.02)	-0.057 (0.014)	-0.002	0.001	-1.48	0.1419
Rocker sole GRF centre of progression: Y length max	0.230 (0.01)	0.231 (0.014)	0.003	0.001	2.35	**0.0199**

5.4.5.1.2 Foot orthoses effect

LASER boot and foot orthoses effect (conditions E and F)

The LASER boot with FFO (LASER intervention) produced a reduction in plantarflexion moment of 0.03 Nm.kg (P=0.043) when compared to the LASER boot alone (Table 35). No differences were reported in ankle dorsiflexion moments and the FFO produced a small increase in eversion moment (0.01 Nm.kg) which was not significant.

Table 35: Exploration of functional foot orthoses effect on the LASER intervention ankle kinetics						
Ankle moments (Nm.kg)	**LASER boot only (E)**	**LASER intervention (F)**	**Condition E v F**			
			Estimate	**Standard error**	**T value**	**P value**
Ankle plantarflexion moment	1.40 (0.17)	1.37 (0.17)	0.03	0.013	2.03	**0.043**
Ankle inversion moment	0.14 (0.07)	0.15 (0.07)	-0.008	0.010	-0.77	0.444
Ankle dorsiflexion moment	-0.43 (0.07)	-0.43 (0.08)	-0.004	0.010	-0.41	0.685
Ankle eversion moment	-0.11 (0.03)	-0.12 (0.04)	0.011	0.007	1.48	0.140

Comparison of the LASER boot without an FFO identified a systematic reduction in all ankle moments when compared to a trainer (Table 36). The LASER boot reduced plantarflexion moment (0.15 Nm.kg, P=<0.001), eversion moment (0.02, P=0.01) and treads towards decrease for inversion moment (0.01 Nm.kg, P=0.61). However, reductions were offset by an increase in dorsiflexion moment of 0.06 Nm.kg which was significant (P=<0.0001).

Table 36: Exploration of ankle kinetic effect of the LASER boot without a functional foot orthoses compared to a trainer						
Ankle moments (Nm.kg)	**Trainer (A)**	**LASER boot only (E)**	**Condition A v E**			
			Estimate	**Standard error**	**T value**	**P-value**
Ankle plantarflexion moment	1.55 (0.17)	1.40 (0.17)	0.15	0.013	11.31	**<.0001**
Ankle inversion moment	0.15 (0.08)	0.14 (0.07)	0.01	0.010	0.51	0.61
Ankle dorsiflexion moment	-0.37 (0.09)	-0.43 (0.07)	0.07	0.012	5.5	**<.0001**
Ankle eversion moment	-0.13 (0.07)	-0.11 (0.03)	-0.02	0.008	-2.47	**0.0144**

Test of fixed effect

Comparison of the LASER boot and trainer and the LASER boot with and without an FFO test of fixed effect was significant for treatment (P=<0.0001). In addition, the ankle dorsiflexion moment period was significant (P=0.04). Sequence and prior treatment did not affect any of the outcome measures.

5.5 Discussion

This study used 3D gait analysis to establish the mechanism of action of the LASER interventions individual and combined components when compared to a standard trainer in a cohort of non-pathological males. In this Williams Latin square designed to study the primary outcome, ankle moments of force were significantly reduced. The LASER intervention appears to exert its main effect on kinetics and kinematics of the ankle joint in the sagittal plane and to a lesser extent at the knee and the hip. Establishing the mechanical effect in a healthy cohort has identified the main effect of the LASER intervention as well as identified parameters that may be affected in pathological cohort with ankle haemarthropathy. These findings support future research in haemophilia as well as other pathological conditions of the ankle joint.

5.5.1 Ankle joint kinetics and kinematics

The primary aim of this study was to determine whether the LASER intervention reduced the mechanical demand on the ankle joint when compared to a standard trainer. The results of this study demonstrated statistically significant changes in ankle joint kinetics and kinematics. The effect of the LASER intervention at the ankle occurred predominantly within the sagittal plane with a significant reduction in plantarflexion moment and a small increase in dorsiflexion moment, therefore decreasing the overall mechanical demand on the ankle joint.

5.5.1.1 Kinetics

The reduction of plantarflexion moment of the LASER intervention (1.37 Nm.kg (SD 0.17)) in comparison to a standard trainer (1.55 Nm.kg (SD 0.17) indicate the combination of the individual components of the LASER intervention (boot, SACH, rocker sole and FFO) are effective at reducing the rotational force at the ankle joint as the foot begins to dorsiflex during the ankle rocker. In the frontal plane no difference between conditions was reported for inversion moment and a small decrease in eversion moment however the difference was not significant suggesting little or no change in frontal plane ankle kinetics. The individual component effect of the SACH modification was effective at reducing plantarflexion moment. Comparison to other studies using SACH modifications are limited, however in prosthetic foot construction report peak plantarflexion of 1.09 Nm.kg of a SACH [322]. This study, whilst not conduct in in-vitro showed low-level evidence to support the effect of the SACH and supports its inclusion in the LASER intervention. Long *et al.* (2007) reports a rocker soled shoe with a similar rocker design to the LASER intervention displayed decreased plantarflexion moment at midstance and whilst peak moments were not reported, there were significant reductions during toe-off between 0.05 and 0.11 Nm.kg [187]. The inclusion of an FFO was a significant contributor to changes in ankle kinetics and justifies their inclusion in the LASER intervention and highlights the potential of FFO to contribute to the overall mechanical effect. The LASER intervention, which included the FFO when compared to the LASER boot alone significantly reduced plantarflexion moment (0.03 Nm.kg) and whilst small in effect the FFO does contribute a positive effect. Findings are similar to Nester *et al*. (2003) who investigated the effect of FFO in a healthy cohort using 3mm EVA insoles with an arch filler and medial/lateral wedging material [90]. The study identified that under normal walking conditions FFO with 10 degrees of rearfoot posting (medial and lateral) produced little effect on sagittal plane kinetics when compared to a shod condition. The data reported in a shod condition only opposes this chapters results, little detail was captured about the participant's foot posture which may have influenced

the FFO effect. Similarly, shoe-mounted markers were used which are known to underestimate foot and ankle biomechanical data [126, 131, 323].

The proposed effect of the SACH is a pseudo-plantarflexion moment in which the SACH compresses during the heel and ankle rocker when the plantarflexion moment occurs as the foot begins to dorsiflex in preparation for heel lift during the propulsive phase of gait [72]. Whilst the ankle is in a closed pack position and at its most stable, pathological changes to the anterior joint line in combination with synovial hypertrophy, a common presentation in ankle haemarthropathy, increase the risk of haemarthrosis and further soft tissue trauma [306]. Therefore the decrease in peak plantarflexion moment produced by the LASER intervention, in theory, reduces the potential for mechanical trauma to soft tissue and bony blocking as a potential source of ankle joint haemarthrosis and pain [293]. Changes in gait pattern have been observed by Lobet *et al.* (2011) in a cohort of severe haemophilia males (n=21) with ankle haemarthropathy. Reductions in peak ankle plantarflexion moments were 1.02 SE0.28 (IQR 0.44-1.62) Nm.kg $^{-1}$ and ROM of 14.4 (SE 3.9 (IQR, 8.4 to 3.9) degrees respectively, highlighting the change in function observed in advancing haemarthropathy of the ankle. Whilst the LASER intervention did not decrease moments to equivalent levels, data was collected in healthy participants so equivalent levels of change would not be expected. Reductions in kinetics were in comparison to a standard trainer that is often worn by patients in clinical practice, therefore providing insight into potential effects. The LASER intervention exhibits characteristics that justify future testing in the haemophilia population and potential therapeutic benefit that accommodates the mechanical and functional changes associated with haemarthropathy [293].

Dorsiflexion moment was higher for the LASER intervention (-0.43 Nm.kg (SD0.08 CI -0.46 to -0.40) than the trainer (-0.37 Nm.kg (SD 0.09 CI -0.40, -0.34) which reached significant (P=<0.0001) The increase in dorsiflexion moment at the ankle were higher in both conditions when compared to the literature, however, healthy participants were used and it is unlikely the same finding would occur in a haemophilia or other pathological

cohort. Long *et al.* (2007) reported very little dorsiflexion moment at IC into weight acceptance by a rearfoot and forefoot rocker footwear but neither change was significant when compared to a standard trainer, therefore, limiting direct comparison [187]. Observations of control footwear in research of negative rocker footwear have reported mean (SD) small increases in peak dorsiflexion moments of (-0.26 Nm.kg(SD 0.05) to -0.09 Nm.kg (SD 0.05)) [193]. The reason for the reduction in the negative rocker was the use of a curved sole at the rearfoot moving the point of contact during the stance phase of gait from the heel towards the midfoot. The Wu *et al.* (2004) study of rocker profiled shoes reported an absence of dorsiflexion moment owing to the design of the footwear which had an increased heel height, a known factor in the reduction of dorsiflexion moment caused by a higher heel to forefoot ratio with a higher heel reducing dorsiflexion moments [194].

The increase of ankle dorsiflexion moment of the LASER intervention, whilst significant were relatively low (0.06 SE 0.01 Nm/kg, $p<0.0001$) and may not impact the clinical management of ankle haemarthropathy. In this chapter, the increase in dorsiflexion ROM resulted in a longer lever arm, away from the ankle fulcrum. GRF was increased at heel strike with both changes producing the increase in ankle dorsiflexion moment. The LASER intervention heel height is similar to the forefoot when the SACH heel is compressed. Therefore increasing heel height may also be beneficial by reducing the dorsiflexion moment and a potential solution in clinical practice, which commonly includes a heel wedge to FFO increasing heel height to “fine-tune” the footwear and orthoses effect. Encouraging results suggest further investigation is needed to establish if the LASER intervention translates to a pathological cohort by reducing the mechanical demand on the ankle. A decrease in dorsiflexion ROM at the ankle may explain findings, therefore increasing the moment arm during the ankle rocker. GRF whilst not directly reported appeared to increase at IC with the LASER intervention which may have contributed to the increase in rotational forces posterior to the ankle. The results of this study represent the potential to increase the eccentric burden of the anterior musculature

during IC. It suggests the anterior muscles would require greater eccentric control during gait. In the management of ankle haemarthropathy, the foot drifts into a plantarflexed position with a reduction of dorsiflexion ROM [8, 79]. Muscular atrophy of the lower limbs is common in the presence of ankle haemarthropathy and therefore rehabilitation may be required to improve eccentric contraction of the anterior ankle musculature during IC to negate any potential increased burden.

5.5.1.2 Kinematics

Sagittal and frontal plane ROM were reduced by the LASER intervention thereby maintaining the ankle joint within a restricted ROM. The secondary and exploratory effect of the LASER intervention and military boot condition, respectively, restricts ankle ROM. A systematic reduction in both sagittal and frontal plane motion was reported with a 3.5 and 1.9-degree reduction in ROM, respectively. Reported reductions in ankle ROM are supported by observational studies of boot stiffness. Changes in boot stiffness between soft and stiff boot uppers restrict ankle ROM 16.71 (SD 3.3) to 18.11 (SD 3.4) between footwear conditions were reported in ankle sagittal plane ROM and frontal plane motion of 9.41 (SD 3.3) to 8.71 (SD 3.3) in boots with a soft and hard shaft respectively [324]. Whilst direct comparisons to this chapter are limited by different boot types and walking conditions, the findings of this chapter provide support to the proposed boot mechanism of action that fixation above the ankle joint reduces ROM. The explanation for the finding may be attributed to the mixture of materials and different footwear components of the LASER intervention that produced the overall effect on ankle kinematics. Machine modelling of boot upper stiffness in small bespoke studies reports the stiffer the boot upper, the less variation in ROM occurring in the sagittal plane. Whist conducted using a robotic foot that does not represent true reciprocal gait pattern in human movement analysis, the study provides insight into this chapters kinematic data [325]. The properties of the boot upper were not measured in this chapter, rather the boot is used in clinical practice at the Leeds CCC to provide some form of restriction whilst allowing a restricted ankle ROM to occur but with a restricted range. Double rocker soled shoes

are reported to reduce ankle ROM in footwear research with reduction in total sagittal plane ROM of between 6.0 and 9.6 degrees [193, 194]. The individual effect of the rocker sole on ankle ROM was not investigated but the combination of current findings and past research on rocker sole footwear suggests the rocker sole as part of the LASER intervention may have contributed to the reduction in sagittal plane ROM.

The military boot accounted for the largest reduction of ankle ROM in both the sagittal (22.8°, SD3.3) and frontal 9.1°, SD1.9) planes (p=<0.0001). The results support the hypothesis that fixation above the ankle reduces variability in ROM and therefore has the potential to have a mechanical effect. During the IC the foot remained in a more plantarflexed position but observed differences were small in effect with similar between condition time curves (Figure 22). Time curves for the LASER intervention followed the same ROM as did the trainer until terminal stance where dorsiflexion occurred, but to a lesser extent in the LASER intervention therefore the ankle joint was less plantarflexed. The above ankle fastening of the ankle boot is clinically important in the management of ankle haemarthrosis for not only its restriction in ROM but the feeling of stability. Ankle haemarthropathy is associated with loss of proprioception around the ankle and therefore the higher fastening may provide greater somatosensory feedback as well as maintaining a limited ankle ROM [326, 327]. The reduction may be interpreted as a negative effect where rehabilitation would aim to maintain full ROM and lower limb strength, but in haemophilia, ROM can be reduced by up to 80% by the third decade of life [79]. In addition, fixation above the ankle may prevent excessive-end ROM in a pathological cohort of patients with ankle haemarthropathy where joint margins and subtalar joint are affected by osteophyte formation and chronic OA [86, 87].

5.5.2 Proximal effect

5.5.2.1 Knee

The LASER intervention produced minimal proximal effect at the knee with similar moments and ROM in the sagittal and frontal planes compared to a trainer. An increase of 0.028 Nm.kg (SE0.006) knee adduction moment was observed in the LASER intervention. Knee biomechanics in adults with haemophilia report maximum knee flexion and extension moment of -0.25 (SD0.09) and 0.53 Nm/kg (SD, 0.12) respectively in developing and established multi-joint haemarthropathy which decline as the disease progresses [135]. Whilst significant, the increase is relatively small in isolation and the clinical relevance of the significance is questionable as to whether such a small change in adduction moment would have a detrimental effect in the haemophilia cohort. The LASER intervention in the frontal plane increased knee ROM by one degree, which was significant (P=<.0001). The clinical significance of this finding makes very little difference to the overall functional effect at the knee. Similarly, changes in knee flexion ROM has been reported at loading response of 12.0 (IQR,7.0;15.9) degrees which are similar to the data reported for the LASER intervention [135]. Therefore the potential to have a positive mechanical effect at the knee in haemophilia as the LASER intervention maintains the knee within acceptable ROM. The level of haemarthropathy at the knee has declined since the introduction of prophylaxis CFC and regular use of treatments but there is still a cohort of individuals where the knee has either been a target joint of haemarthropathy, or the lack of previous treatment means the knee has significant joint changes with loss of ROM and flexion deformity [9]. The use of the LASER intervention in the presence of knee haemarthropathy requires further evaluation to establish whether the use is suitable for the presence of both knee and ankle haemarthropathy. The decreased ROM suggests the reduction in required ROM may prevent end ROM and the mechanical joint stresses that are detrimental to treatment and patient reported outcomes. Therefore in the presence of knee joint pathology, the LASER intervention should be closely monitored.

5.5.2.2 Hip

Changes reported in hip kinetics and kinematics were very small in magnitude despite significance in hip extension and adduction moments. Advancing haemarthropathy of the ankle is associated with an increase in the recruitment of the hip flexors as patients adapted their walking pattern to accommodate for the loss of ankle ROM [136]. Lobet *et al.* (2010) observation of hip peak extension moment during the stance phase of gait of 0.47 (SD 0.12) $Nm.kg^{-1}$ during the early stance phase of gait [135]. Therefore when prescribing modified footwear and FFO in the management of ankle haemarthropathy, acknowledgement of the potential proximal effect on the hip should be taken into account. Whist comparability to this chapters data is experimental and undertaken in healthy controls, the proposed mechanism by which the LASER intervention exerts its effect on the hip presents a positive finding. The potential to produce large proximal changes in hip kinetics and kinematics were a concern in this chapter owing to the multi-joint nature of severe haemophilia and the inherent risk of causing soft tissue and joint bleeding by producing biomechanical changes at the hip [113, 135]. However, the proximal effect of the LASER intervention was minimal.

5.5.2.3 Ground reaction forces

Observation of GRF was similar between conditions with similar vertical GRF time curves (Figure 25a) between conditions with the LASER boot slightly higher (0.03 force/body weight) which was significant. However, both conditions fell within normative data sets of 1.2 force/ body weight [91, 92]. Medial and lateral forces were reduced by the LASER intervention with differences occurring in the early part of stance (0-20%). Again there were significant changes in anterior and posterior (Figure 25c) forces but these were very small in magnitude with force-time curves similar between conditions. Results indicated that there is a minimal clinical difference between conditions and whilst findings were significant for several of the variables the increase was less than 0.03 force/body weight for all GRF outcomes (Table 30). The LASER intervention, therefore, produced minimal changes to GRF with the modifications maintaining normal GRF acting on the

foot and ankle during the stance phase of gait. This finding supports the direction of change that the mechanical changes produced by the LASER intervention mainly occur at the ankle joints whilst maintain normal biomechanical features of gait.

Observations of progression of GRF CoP would hypothesize that the rocker sole of the LASER intervention would increase the length of the CoP trajectory as the compensatory effect of the rocker means the shoe surface is in contact with the ground for longer. Clinical significance of the change in all GRF parameters was relatively small in magnitude with differences not exceeding 0.01cms across all despite significance (P=<0.01) in all but the minimum GRF CoP in the frontal plane. Therefore the rocker soled shoe did not have a large effect on GRF CoP compared to the trainer. Observation of in-shoe pedography in haemophilia has shown a large variance in the progression of CoP in patients with established ankle haemarthropathy [176]. The use of FFO in the study stabilised the CoP trajectory providing stability and decreasing medial and lateral CoP variability. Whilst no formal data were reported, CoP trajectories displayed less variation in medial and lateral displacement and significant reduced spontaneous joint bleeding (P=<0.001) over six months [176]. Exploratory results for the mechanical effect of the rocker sole may therefore be isolated to the ankle kinetics and kinematics. Observation of GRF CoP data in a pathological cohort is needed to understand the mechanism of effect in patients with haemophilia as the FFO used may reduce medial/lateral CoP variation.

5.5.2.4 Temporal and spatial outcomes

Walking speed, cadence and double support were all reduced by the LASER intervention except for step length which was similar when compared to the trainer. The clinical relevance of these findings whilst significant, represent very small differences between the LASER intervention and the trainer that clinically would not be considered meaningful. In a cohort of patients with ankle haemarthropathy, the very small changes may be accounted for by the in-between session or condition variance. Findings are a

limitation to observation in healthy controls where changes in function are less apparent. Wu *et al.* (2004) reported reductions in healthy participants wearing a modified double rocker shoe with a SACH 104.8 step/min (SD 7.2) and 107.5 (SD 4.1) in a standard shoe. Small, non-significant reductions were also reported in walking speed for standard footwear 0.98 (SD 0.11) step/min compared to a rocker soled shoe 0.97 (SD 0.91) m/s which supports the suggestion that the use of healthy controls may not capture the functional effect on temporal and spatial parameters [193]. In haemophilia cohorts, temporal and spatial parameters are reduced in adults with ankle haemarthropathy. Comparison to a control group with haemophilia without ankle haemarthropathy reported small variations in cadence (109.9/109.5 step/min, p=0.847), step length (0.72/ 0.75m, P=0.092), and stance time (64.8% vs 64.1% P=0.01) [113]. Therefore the significant differences reported for the LASER intervention are not clinically large enough to raise concerns about the potential for the reduction in function during gait.

5.5.3 Limitations

5.5.3.1 Carryover (period) effect

The Williams Latin square design within-subject test of fixed effects allowed the identification of carry-over effect (period) from the previously used footwear condition and whether the order in which footwear condition order (sequence) affected data collection [313]. In general, there was minimal effect except for the footwear condition itself (treatment). The exceptions were peak dorsiflexion moment, peak ankle dorsiflexion/ plantarflexion ROM, hip abduction moment and anterior/posterior GRF, all of which were significant for carryover (period). This period or carryover effect means the previous condition tested may have influenced the intervention. The between conditions effect may have therefore affected these parameters and results should be interpreted with caution. The explanation for the carryover effect may be attributed to an inadequate washout period whereby the participant did not have sufficient time between testing footwear conditions to adapt to the different footwear types. A pragmatic approach was

taken to the amount of time spent between conditions, owing in part to the large amount of data collected in the study session. Allocation of a five-minute washout period was based on previous research in barefoot and shod footwear conditions undertaken previously within the host research institution [127]. Future footwear studies may not use as many (six) footwear conditions allowing for a longer wash out period between footwear conditions. The structure of the LASER intervention may require a longer period of adapt especially in a pathological cohort where mobility is affected. Therefore increase in washout time between conditions may be more achievable in future LASER intervention studies.

5.5.3.2 Outcomes

The gait parameters were analysed during the stance phase of gait. Whilst the measurements of kinetic parameters were appropriately reported over the stance phase of gait, the inclusion of swing phase (approximately 40% of the gait cycle) may have provided information as to the LASER intervention effect during unloading such as the effect of the weight of the boot on the knee and hip kinematics [91]. Whist the primary outcome of the LASER intervention were ankle kinetics, technical difficulties with the capture ability to track 3D markers during terminal swing in all of the footwear conditions resulted in the exclusion of swing data. The set-up of the Chapel Allerton Hospital, Leeds gait laboratory camera system was static to allow the collection of multiple datasets including stairs and slope walking for several concurrent PhD projects. Future studies would benefit from the ability to model the full gait cycle by repositioning cameras to optimise marker tracking or the use of upgraded camera systems that have more robust tracking technologies. The weight of the LASER intervention may increase the burden of the contralateral musculature of the knee and hip during the swing phase of gait as the knee acts as a pendulum during swing [328]. Whilst we did not measure the difference in weight between the LASER intervention and trainer, the materials used in adaptation make the boot heavier. Evaluation of swing in patients with haemophilia may provide further information on the potential to increase the burden on hip and knee musculature

and potentially increase the risk of trauma, though in clinical practice no increased risk of bleeding has been observed even anecdotally. The primary outcome of this study was ankle moment of force in the sagittal plane during the stance phase of gait and therefore exclusion of swing phase did not affect the study design. In pathological gait, the inclusion of swing may provide insight into the contribution of footwear weight and structure on the proximal joints, especially in the presence of multi-joint pathology and associated muscle atrophy common features of joint haemarthropathy in haemophilia [135]. Data were analysed statistically using peak values, a common method of reporting biomechanical data where conventional analyses require a single data point for each participant. However, the full biomechanical dataset consists of a time series and the use of a single time point within the gait cycle may exclude the magnitude of change over the period of interest, which in this chapter was the stance phase of gait. A small number of recent biomechanical studies have adopted the evaluation of gait data over the full gait cycle [329, 330]. One such method, Statistical Parametric Mapping (SPM) has been used to identify at what point in the gait cycle changes occur and magnitude [329, 330]. The use of SPM is a novel introduction and was beyond the scope of this thesis, however, a future study in a haemophilia population using SPM may provide a more meaningful interpretation of biomechanical change in a condition characterised by multi-joint haemarthropathy and changes to ankle joint structure and function [84].

5.5.3.3 Foot model

An inverse dynamic model was used with a single segment foot model to capture in-shoe data. Multi-segment foot modelling is preferred when investigating and understanding how different segments of the foot move when walking. However, a pragmatic approach was taken to capture data in-shoe with a focus on maintaining the integrity of the LASER intervention and isolation of a single segment model allows the quantification of ankle kinematics. The balance between assessing interventions vs the loss of shoe integrity is associated with cutting multiple windows for the collection of a multi-segment foot model. The use of a multi-segment would have required cutting multiple holes into the boot and

therefore jeopardise the structural integrity of the boot and incorporate bias into data collection [20]. Future observational studies may benefit from assessing structural changes to footwear properties before evaluation in clinical studies. In addition, were developing multi-segment foot models for use in-shoe validation should be undertaken to establish the optimum marker set for modelling ankle kinematics whilst maintain footwear integrity. More than four windows cut into footwear has also been shown to jeopardise the integrity of footwear during footwear evaluation and whilst military footwear is significantly more structured increasing the number of windows to allow another marker would not have increased the reliability of data collected [130].

5.5.4 Implications of findings

The current findings indicate the LASER intervention produce beneficial changes to the kinetic and kinematic profile of the ankle joint whilst minimising the proximal effects at the knee and hip during the stance phase of gait. The individual and combined effect of the LASER intervention conditions have been established and the primary outcome of ankle moments of force was mostly reduced by the intervention and therefore represent a decrease in the mechanical burden of the ankle joint. The implications for our findings provide an understanding as to the potential clinical effect in a cohort of normal healthy males. The methods used in this chapter to model the foot in-shoe have been shown that an in-shoe foot model can be used to report ankle kinetic and kinematic data. Therefore a future study in pathological males with ankle haemarthropathy may be undertaken before a full RCT.

5.5.5 Conclusion

The LASER intervention significantly improved the kinetic and kinematic profile of the ankle joint during the stance phase of gait. The mechanism by which this combination of primary footwear components have been confirmed and establish that the effect hypothesised in clinical practice has the desired effect. Whilst this study has been conducted in healthy adult males, our findings provide a basis for investigation in pathological cohorts before a future RCT. The in-shoe modelling technique used in this study is effective at reporting ankle kinetics and kinematics and therefore should be considered or adapted to a multi-segment intervention model. Future studies should be conducted in haemophilia cohorts and other diseases affecting the ankle to establish whether the LASER intervention improves HRQoL, foot and ankle pain and the prevalence of haemarthrosis.

Chapter 6 - Discussion, future directions and conclusions

Several gaps identified in current literature have been addressed by the work presented in this thesis. The prevalence of haemarthrosis and concurrent joint health are commonly reported as total annual bleed rates (ABR) and annual joint bleed rates (AJBR) without reference to individual joint health. This thesis has now reported the prevalence and incidence of joint bleeding and concurrent musculoskeletal health. Ankle haemarthropathy is a common feature of haemophilia and is cited as the most affected joint in terms of haemarthrosis and joint disease. The impact of ankle haemarthropathy on health-related quality of life (HRQoL), and foot and ankle patient-reported outcome measures (PROM) has been identified. The use of footwear and functional FFO have the potential to reduce the burden of ankle joint haemarthropathy, however, there is little evidence to support their use in clinical practice, nor has the mechanism by which foot and ankle interventions exert their mechanical effect. The LASER interventions mechanical effect has been established as a potential therapy for the management of ankle haemarthropathy.

6.1 Thesis Synopsis

This thesis aimed to explore the prevalence and impact of ankle haemarthrosis and the resultant haemarthropathy, whilst providing a better mechanistic understanding for the use of existing targeted footwear and FFO intervention. The observed outcomes of this thesis are summarised in Chapters Three, Four and Five: the prevalence and incidence of haemarthrosis and concurrent joint health; the impact of haemarthropathy on health-related quality of life and foot and ankle specific outcome measures; and the kinetic and kinematic mechanism of action of the Leeds Ankle Stabilising Enhancer Rocker (LASER) intervention.

Chapter Three - The prevalence of ankle haemarthrosis in moderate and severe haemophilia A and B

This chapter aimed to identify the prevalence of ankle haemarthrosis and concurrent joint health in severe haemophilia A and B. Data obtained from the National Haemophilia Database (NHD) identified 176 individuals compliant with prophylaxis and had a concurrent haemophilia joint health score (HJHS).

- This NHD database study identified that despite compliance to treatment, 60% of adults had a minimum of one bleed during the 12 month study period.
- Despite 30% of participants using extended half-life (EHL) clotting factor concentrate (CFC), AJBR have changed little since the last NHD evaluation in 2015.
- The ankles were disproportionally affected by haemarthropathy, with higher HJHS than the knees and elbows.

Chapter Four - The impact of blood induced ankle arthritis in patients with moderate and severe haemophilia A and B: The HAPII study

This chapter aimed to provide insight into the impact of haemarthropathy on health-related quality of life (HRQoL) and foot and ankle specific patient-reported outcome measures (PROMs). The analysis included 243 participants with moderate and severe haemophilia A and B and a consultant diagnosis of ankle haemarthropathy. Patients were recruited from haemophilia comprehensive care and haemophilia treatment centres across England, Wales and Scotland. A concurrent consultant survey obtained details of service provision at 43 haemophilia centres across the UK and then compared them with the patient impact questionnaire responses.

- HRQoL and foot and ankle PROMs are poor in the presence of ankle haemarthropathy regardless of haemophilia type, severity or treatment regime.

- Pain was a significant feature of ankle haemarthropathy and the main contributor to poor HRQoL and foot and ankle PROMs.
- Findings indicate that Numerical Pain Rating Scales (NPRS) of ankle pain over the past six months may be an independent predictor of worsening HRQoL and foot and ankle PROMs.
- The use of pharmacological pain medication was low despite multi-joint haemarthropathy and chronic levels of ankle joint pain.
- The consultant survey reported access to a range of complementary musculoskeletal (MSK) services in UK haemophilia centres including those for foot and ankle problems. In comparison, patient responses to the impact questionnaire indicate that patients did not access footwear and orthotic services.

Chapter Five - A mechanism of action study to explore the individual and combined components of the Leeds Ankle Stabilising Enhanced Rocker (LASER) boot and FFO (LASER intervention)

This chapter aimed to investigate the mechanism of action of the LASER intervention. Three dimensional (3D) gait analysis was undertaken in 36 healthy male participants to establish the effect of the individual and combined components of the LASER intervention on the ankle joint and proximal lower limb joints.

- The LASER intervention significantly reduced plantarflexion moment of force at the ankle joint compared to a standard trainer.
- The proximal kinetic and kinematic effects of the LASER intervention on knees and hips were minimal.
- Individual effects of the LASER component features; the solid ankle cushioned heel (SACH), rocker sole and military boot were found, producing the proposed effect for all conditions when compared to a standard trainer.

- FFO significantly reduced ankle joint moments when used with the LASER boot.
- The preliminary evidence of efficacy and therefore safety of the LASER intervention findings in healthy males justify future research to determine the efficacy and effectiveness when used in a cohort of haemophilia patients with ankle haemarthropathy.

6.2 Thesis discussion

6.2.1 Prevalence of ankle haemarthrosis and concurrent joint health

Patients with severe non-inhibitor haemophilia who were compliant with prophylaxis reported a minimum of one bleed in 60% of haemophilia A and 40% of haemophilia B patients over the 12 month study period [4]. The small numbers of haemarthrosis episodes in the prevalence data are low across the most affected joints of the ankles, knees and elbows. In Chapter Three, our findings indicate that despite improvements in treatment, only minor improvements in haemarthrosis are reported with similar AJBR (1.0, IQR 0.0;4.4) and 40% haemarthrosis free to Scot *et al.* (2019) who three years earlier reported a median AJBR of 1.0 (IQR 0.0;4.0) with only 34% joint bleed free three years earlier [4]. The findings of this chapter highlight the difficulties in preventing all incidents of haemarthrosis, even where treatment compliance is deemed good. The rates of AJBR were low, but it appears that achieving zero incidents of haemarthrosis under current CFC treatment regimens are not achievable. The balance between obtaining adequate trough levels, risk of complications such as inhibitor development and the burden of regular infusion to patients represent challenges in obtaining adequate prophylaxis [1, 4]. The prevalence chapter adds to the data on compliant patients, however, it raises questions as to the true UK prevalence of patients who fall below the UKHCDO NHD compliance threshold for reporting disease statistics. If the most compliant still experience haemarthrosis it is likely that the true clinical landscape of the cohort below the threshold for the report is worse. It, therefore, remains unclear as to the

true UK prevalence and incidence of haemarthrosis and this thesis has highlighted the need for a better understanding of the UK haemophilia AJBR and the effect on joint health.

The relatively low prevalence of joint haemarthrosis may be clinically acceptable under current treatment regimens, however, a single incident of haemarthrosis with even low quantities of blood within the joint is known to produce pathological changes in cartilage, with blood products at levels as low as 10% initiating an inflammatory process and synovitis at two days after exposure [62]. Therefore even a single detectable joint bleed may be enough to initiate a cascade of pathological joint changes. In joints already affected by joint disease, this single incident may be more significant as the joint is burdened longer-term by haemosiderin deposition, synovial hypertrophy and cartilage damage [237-239]. The progression of joint disease often leads to changes in joint structure and function as haemarthropathy progress. The ability to distinguish between an incident of haemarthrosis or joint pain becomes more difficult as joint health declines, especially at the ankle where clinical detection of joint health decline is often delayed [272]. The concept of subclinical bleeding has gained more traction as the AJBR decline, however, joint damage continues, but there is yet to be any definitive evidence to support this hypothesis [253]. Therefore the disproportionate level of ankle haemarthropathy reported in the prevalence Chapter Four raises further questions as to the mechanism by which joint health declines. These findings highlight the complexities of monitoring bleed history and establishing joint haemarthrosis status where data is often self-reported. Confirmation of bleeding is often confirmed with use of extra CFC to arrest symptoms, which is more complex in the presence of haemarthropathy whereby it becomes ever increasingly difficult to distinguish between chronic joint pain and bleeding events [271]. Therefore in the absence of a significant debilitating ankle haemarthrosis, repeated low level non-detectable joint haemarthrosis may occur and explain the long term deterioration of ankle joint health.

In Chapter Three, 30% of patients used EHL treatment which is reported to decrease annual bleed rates by 20 to 50% whilst maintaining factor VIII and IX level half-life by 1.5 to 1.6 times longer than standard half-life (SHL) treatment [241, 242]. The first published guidance for use of EHL was published by the UKHCDO in 2016 [331]. Use of EHL in 2017 UKHCDO bleed statistics report indicating EHL accounted for 2.9% of FVIII treatment and by 2018-19 this had increased to 15.6% [232]. From the 2018-2019 Chapter Three prevalence data it is not clear from the outcomes in this thesis whether EHL products reduced joint haemarthrosis, as only minor reductions were identified when compared to previously cited research [4, 13]. The sample of EHL product users in Chapter Three was higher than UKHCDO bleeding statistics, however, this did not influence our results. With such low and unchanging levels of ankle haemarthrosis reported in both Chapters Three and Four, the use of EHL CFC in patients with moderate to severe levels of ankle haemarthropathy appears to reduce the frequency of CFC infusion only [226, 241] rather than improving joint health.

The findings in Chapter Three are reported 12 years after Stephensen *et al.* (2009) who identified that the ankle had become the most commonly affected joint for incidents of haemarthrosis in a small cohort of boys with severe haemophilia A [9]. Prevalence data collected in addition to this thesis identifies that children with a median age of 11 (IQR 7;14) (n=97), with severe haemophilia and compliant with prophylaxis, report bleed prevalence of 33% and 60% in haemophilia A and B, respectively [244]. The AJBR at all joints were very low with a median (range) AJBR of 0.00 (IQR 0.00; 0.00). Levels of clinically detectable haemarthropathy were similarly low, with a median HJHS of 0.0 (IQR 0.0; 0.0). These results suggest that current treatment regimens in children are either effective at reducing bleed rates to a point where joints are not affected by haemarthropathy or they are not detectable until later years. Patient-reported haemarthrosis levels in Chapter Five were similar to the levels reported in the prevalence chapter (Chapter Three) with mean ankle AJBR between 0 (SD 3.0) and 2.0 (SD 4.0) in haemophilia A and B respectively, on prophylaxis and on-demand treatment. Ankle

AJBR were higher in moderate disease with a mean of 1.0 (SD 3.0) in moderate haemophilia A on prophylaxis and a mean of 4.0 (SD 0.0) on-demand treatment. The similarities in AJBR in the severe haemophilia A prophylaxis groups across the prevalence and impact studies provides insight to incidence of ankle joint haemarthrosis in the general population of severe haemophilia with different treatment regimens and associated joint disease in patients who may vary in their treatment compliance and regimes.

A recent publication by Collins *et al.* (2021) on UKHCDO guidelines for the management of severe and moderate haemophilia recommends that prophylaxis is initiated in any moderate patients who experience a single haemarthrosis, or a clinically significant bleed [253]. Where trough levels are between 1-3 IU/dL patients should be treated the same as those with severe haemophilia, with prophylaxis offered and a treatment target of above 3 IU/dL or to a level that halts spontaneous or breakthrough bleeding [253]. The significance of this recommendation is a step towards reducing the burden of joint disease not only in severe haemophilia but by way of recognition that even moderate haemophilia can make a significant contribution to the complications of bleeding [5, 29, 253, 332]. Chapter Three finds that patients with moderate haemophilia have similar bleed rates and ankle joint disease to severe haemophilia adds to the emergence of data indicating better target management of moderate haemophilia is required to reduce the patient burden of disease both physically and mentally. The number of moderate haemophilia cases in our cohort was small (n=29) therefore drawing meaningful inference from the results is not possible, but similarities in disease characteristics of severe haemophilia provide insight into the incidence of haemarthrosis and the progression of joint haemarthropathy at the ankle. Whilst HJHS was lower in patients with moderate haemophilia when compared to those with severe haemophilia, ankle AJBR were higher indicating that those with moderate haemophilia have delayed levels of ankle joint haemarthropathy. It remains unclear as to whether those with moderate haemophilia have the same intensity of bleeding as severe disease or rate of joint health

decline, but new findings provide insight into the increased incidence of haemarthrosis where ankle joint haemarthropathy is less detectable [253]. The data presented in the prevalence and impact chapters (Chapters Three and Four) indicate that regardless of prophylaxis or on-demand treatment regimens, the levels of ankle haemarthropathy correlate to radiological levels of moderate to severe joint damage.

Examination of arthropathy at all joints indicate that in the presence of ankle haemarthropathy, distribution of multi-joint osteoarthritis (OA) at the hips, shoulders, wrist and hands were similar to OA cohorts, but develop up to a decade earlier [251]. It is unclear whether the earlier reporting of joint arthropathy is related to haemarthrosis, or rather changes in joint health are caused by muscle atrophy and altered joint biomechanics [333]. Increases in life expectancy mean that those with severe haemophilia are now living to a similar length of life as the general population. However, concerns are emerging to the levels of disability experienced in older adults with haemophilia. Patients aged over 65 who did not have access to CFC through childhood are reported to have between four and six joints affected by haemarthropathy (ankles, knees, elbows) [334]. Established joint disease in combination with low bone mineral density is associated with worsening progression of multi-joint haemarthropathy therefore the findings in this thesis present trends towards a similar decline in the younger adult haemophilia population [335, 336]. Chapter Three highlights the importance of monitoring and preservation of joint health not only at the most common sites of haemarthrosis but the examination and reporting of all joint health in haemophilia to ascertain the global effect of haemarthrosis and subsequent disability.

6.2.2 Impact of ankle haemarthrosis and haemarthropathy

This thesis has identified that in the UK haemophilia population ankle haemarthropathy leads to poor HRQoL and foot and ankle PROMs, driven by chronic pain, the decline in physical function and difficulties with social interaction. Haemophilia type, severity and treatment regime were not independent predictors of worse HRQoL or decline in foot

and ankle PROMs. The exception was haemophilia severity and the HAEMO-QoL-A domain of physical function, which indicates that severe patients are impacted during activities of daily living [200]. Observations of HRQoL suggest that impact is correlated with haemophilia severity, with severe haemophilia patients the most affected by the decline in HRQoL when compared to those with moderate and mild disease [221, 246]. Similarly, in haemophilia B, frequency, intensity and levels of haemarthropathy are lower than in patients with haemophilia A [256]. This aligns with previous suggestions that patients with moderate haemophilia A/B and patients with haemophilia B would have better health HRQoL [234, 256]. This thesis reports that despite physical factors that may reduce the impact on HRQoL, haemophilia type, severity and treatment regimen made little difference to HRQoL.

Foot and ankle PROMs scores were similar between haemophilia types, severities and treatment regimes. MOXFQ total score and individual domains of walking/standing, pain and social interaction were all poor, with similar MOXFQ scores to patients undergoing ankle fusion and total ankle replacement surgery, indicating significant chronic pain and disability [267]. Few studies have directly reported foot and ankle PROMs in haemophilia. In the only two footwear and FFO studies that have taken place, the Foot Function Index (FFI) and Foot Function Index Revised (FFI-R) scores reporting moderate levels of haemarthropathy correlated with moderate impact [14, 175]. Higher ankle HJHS and the correlation with higher levels of the joint disease reported by patients in Chapter Four may explain why foot and ankle PROMs scores were more impacted than studies of other haemophilia cohorts with ankle haemarthropathy. Pain was the most prominent feature of ankle haemarthropathy in both HRQoL and foot and ankle PROMs. The use of an NPRS measuring average ankle pain over six months was found to be an independent predictor of all HAEMO-QoL-A and MOXFQ subscales. Therefore average ankle pain over six months, measured using an NPRS has the potential in clinical practice to monitor the impact of ankle joint haemarthropathy and predict worsening HRQoL and foot and ankle outcomes. At what point on the NPRS scale constitutes

decline is yet to be established, however, data captured in Chapter Four identified NPRS of 4.8 (SD 2.7) correlated with the decline in individual and total domain scores of the HAEMO-QoL-A and MOXFQ. The use of the NPRS has the potential to be used at other joints affected by haemarthropathy and whilst the NPRS would not replace outcome measures, it has the potential to be used in clinical practice as an indicator for use of more detailed HRQoL and foot and ankle PROM tools.

Over 50% of patients did not use regular analgesia in the management of acute and chronic ankle pain. The use of analgesia is below levels reported in similar research of haemophilia and chronic joint pain in the United States of America (USA), where up to 76% of patients reported using analgesia and 56% of adults with haemophilia reported opioid use [250]. It is not clear why such a low proportion of haemophilia patients did not use analgesia in our study. In haemophilia, it has been suggested that patients adopt coping strategies to deal with pain such as exercise, massage and distraction techniques [268, 272]. The management of pain in the haemophilia community is reported to be poor, with 40% of patients reporting difficulty in obtaining appropriate pain management from their healthcare provider [271]. Surveys of pain management in adults aged between 40 and 65 years with multi-joint haemarthropathy indicate a lack of access to pain relief for the majority of their childhood where joints were more prone to acute painful episodes of haemarthrosis [334]. Therefore coping with high levels of pain and managing without pain relief is synonymous with chronic haemarthropathy [334]. The findings in this thesis raise valid questions as to the management of pain in haemophilia and the need for targeted pharmacological and non-pharmacological interventions, especially in multi-joint haemarthropathy, where the ankle has been reported to account for 45% of all joint pain [250]. A recently published systematic review of the management of pain using physiotherapy interventions, suggests studies are lacking methodologically, and specifically in their trial designs, to make any conclusive recommendations for pain management [337]. Similarly in the management of ankle haemarthropathy, there is low-

quality evidence that suggests FFO and footwear reduce pain, but no conclusive evidence to change guidance or management [14, 175, 176].

Results from the Chapter Four consultant survey of clinical services available to patients with ankle haemarthropathy indicated direct or indirect access to a range of MSK services such as orthopaedics and rheumatology. Point of care MSK ultrasound (POCUS) provides a cheap and reliable method of monitoring joint health in haemophilia [35]. However, 43% of centres reported no access to the service. The use of POCUS in the management of ankle haemarthropathy is particularly sensitive to detecting soft tissue changes such as synovial hypertrophy, although is limited in the detection of subchondral bone changes due to limited access to the ankle joint and therefore only useful in monitoring joint margins [282, 283]. Therefore haemophilia centres without POCUS access limit the potential for rapid assessment of acute haemarthrosis and monitoring of joint health [280].

When the consultant survey responses were compared with the patient impact questionnaire, the use of footwear and FFO services were somewhat different. The consultant survey indicated access to orthotist service for footwear and ankle brace provision at all centres. In the impact study, 88% (n=211) of patients did not use adapted shoes and only 51% (n=117) used FFO. Access to a podiatrist for MSK assessment and provision of FFO was also available, but the patient's responses for the impact questionnaire indicated only 58% (n=139) patients had access to a podiatrist and only 34% (n=81) were supplied with FFO by a podiatrist.

It was unclear why the uptake of both modified footwear and FFO was low. Studies of footwear and FFO efficacy in a Belgian cohort report good patient satisfaction, with 63% of patients reporting significant reductions in FFI-R pain domain (P=0.007), and improvement in patient comfort, however, there was little effect on ankle kinetic or kinematic measures [14]. This study was underpowered, however, the authors concluded that FFO may be beneficial to patients with moderate levels of ankle

haemarthropathy and suitable for severe ankle haemarthropathy. This may explain to some extent the low uptake of FFO in the Chapter Four patient questionnaire. In the UK, two haemophilia centres have combined physiotherapy and podiatry clinics that provide footwear and FFO services; they reported high levels of patient satisfaction [15, 16]. Research on the effects of FFO have previously reported large reductions in bleed rates, improvement in patient-reported QoL and improved foot and ankle outcomes, but are limited to quasi-experimental and observational studies and date there has been no full RCT [14, 175, 176, 338]. Whilst use of FFO was low in our patients at the Leeds Comprehensive Care Centre (CCC), combined podiatry and physiotherapy clinics use FFO and have reported reductions in pain, increased mobility and less burden of ankle joint disease [15]. This thesis has highlighted the need to understand how FFO and footwear may benefit patients with ankle haemarthropathy and the need to monitor the use in haemophilia care. Establishing the efficacy of FFO in ankle haemarthropathy is required before any definitive conclusions can be drawn.

6.2.3 Mechanism of action of the Leeds Ankle Stabilising Enhanced Rocker (LASER) intervention

Chapter Five aimed to understand the mechanisms of action of the LASER intervention. The novel approach used to capture in-shoe kinetic and kinematic measures has given an insight into the overall mechanical effect of the LASER intervention and the relative contributions of its component feature using William's Latin square approach.

Comparisons between the LASER intervention and a standard trainer identified significant reductions in the internal plantarflexion moment with little change in frontal plane kinetics. Similarly, ankle ROM in the sagittal and frontal planes was reduced by the LASER intervention. Reduction of plantarflexion moment represents a decrease in the rotational force at the ankle during the second ankle rocker as the foot reaches maximum dorsiflexion [293]. Dorsiflexion ROM at the end of the ankle rocker and prior

to initiation of the forefoot rocker prevents end ROM dorsiflexion The clinical significance of finding in ankle haemarthropathy represents the potential to reduce mechanical demand on the anterior ankle joint line as GRF is closer to the ankle joint and the requirement for dorsiflexion is reduced and, in turn, the potential to reduce the effect of bony blocking caused by joint margin osteophytes and limit the risk of soft tissue trauma. Footwear modifications used in the LASER intervention contributed to the overall effect with the SACH reducing the moment as the heel makes contact with the ground. The use of a SACH has been limited to simulator testing in prosthetic feet but support the proposed mechanical effect that a SACH would reduce plantarflexion moment [322]. Long *et al.* (2003) reported an overall reduction of plantarflexion moment of between 0.5 and 0.11 Nm.kg compared to standard footwear using a double rocker sole similar in design to the LASER intervention [187, 194]. Therefore the double rocker soles used in the LASER intervention may have contributed to the overall reduction of plantarflexion moment.

Reductions of the LASER intervention sagittal plane (21.7 SD 3.7) and frontal plane (SD 1.8) ROM in comparison to a trainer support the hypothesis set out in Chapter Five that the LASER intervention would restrict ankle ROM and therefore reduce the mechanical demand on the ankle joint. Restriction in ankle ROM is beneficial in progressive ankle haemarthropathy as the joint structure and function changes ROM becomes altered by plantarflexion deformity and the control of movement is altered by muscle atrophy. The remaining ankle ROM movement may be inhibited, or lack control, therefore exposing the ankle joint to further risk of pain and bleeding. Increases in frontal plane motion have been reported as a compensatory mechanism in ankle haemarthropathy. The reduction in frontal plane ROM produced by the LASER intervention which includes an FFO is a similarly important finding [8, 339]. Disease of the subtalar joint has been reported in 50% of patients in haemophilia. Although this may be a conservative estimate, the biomechanical effect on the ankle joint has the potential to increase the biomechanical burden on the joints adjacent to the ankle joint. Therefore the restriction of ankle ROM

by the LASER intervention which included an FFO may prevent frontal plane corrections and facilitate movement by use of the rocker sole during the three ankle rockers.

The use of an FFO in the LASER intervention produced a reduction in ankle plantarflexion moment. In clinical practice, FFO are adapted with additional materials that change how forces act upon the shoe foot interface [17, 20]. However, Nester *et al.* (2003) evaluation of FFO using a similar design to the FFO used in the LASER intervention demonstrated little effect on ankle kinetics [90]. This suggests that the shoe-mounted single segment kinetic model used by Nester et al. (2003) under-reported ankle kinetics, or the device did not exert an effect on ankle complex moments. Direct comparison of the findings presented in this thesis and those of Nester *et al.* (2003) are limited by advancements in biomechanical modelling in the interim, specifically the use of an in-shoe foot model in Chapter Five. In haemophilia, combined footwear and FFO interventions in chronic ankle haemarthropathy have reported that FFO does not affect ankle kinetics or kinematics, but this study as with Nester *et al.* (2003) used a shoe-mounted marker set, a known source of error in the measurement of foot function [14]. In common with other cited research that shoe-mounted marker sets under-report ankle kinetics and kinematics, with over-reporting in the Chapter Four pilot study. While differences were minor a foot-mounted marker set provides the most accurate method of reporting in-shoe ankle kinetics and kinematics [126, 131, 323]. More research is needed to determine the effect of the FFO effect using in-shoe foot modelling and therefore when designing intervention studies the ability to model the foot in-shoe should be considered to obtain an optimal measurement of mechanical effects.

The proximal effect at the knee and hip kinetics were isolated to the knee adduction moment and at the hip extension and adduction moments. Variations in ROM at the knee were small in effect and whilst reaching statistical significance would not be clinically meaningful. The implications of the finding suggest little proximal effect, however the

multi-joint nature of the haemophilia warrants observation in subsequent studies to ensure the current mechanical results are transferrable to a pathological cohort.

The findings in Chapter Five provide evidence of the mechanical effect of the LASER intervention as a potential therapeutic mechanical device in the management of ankle haemarthropathy. The LASER intervention has now been used in the Leeds CCC for the past decade with reductions in patient-reported pain, disability and AJBR [15, 297]. Better understanding the mechanical effect of the LASER intervention justifies formally testing further in a pathological group of patients with ankle haemarthrosis. The methods used in this chapter have highlighted parameters that may have implications relating to the proximal biomechanical effect of the LASER intervention and identify modifications that may have clinical relevance to pathological gait in future biomechanical intervention studies. Repeating the biomechanical methods used in Chapter 5 comparing haemophilic patients current footwear against the LASER intervention would provide mechanical justification for a larger intervention study in the haemophilia population. A repeated biomechanical study in the haemophilia population would allow observations of changes in the kinetic and kinematics at the ankle and proximal joints reported in Chapter Five to be confirmed before a future RCT. The design of a full RCT with embedded feasibility study would benefit from the inclusion of patients with moderate and severe haemophilia types, treatment regimens and details of pharmacological treatment (type, dose and trough levels) with varying levels of ankle haemarthropathy and should include details of multi-joint haemarthropathy to capture effect. The inclusion of HRQoL and foot and ankle PROMs similar to the outcomes used in Chapter Four would provide a measure of the non-biomechancal impact of the intervention, as well as allow comparison to other diseases that affect the ankle joint.

The improvement in ankle kinetics and kinematics produced by the LASER intervention represents a potential for therapeutic benefit in the management of ankle haemarthropathy. In haemophilia haemarthrosis are associated with a decline in joint health structure and function that becomes a source of pain and disability as joint health

declines [8, 135]. Therefore the LASER intervention has the potential to provide a means of facilitating the ankle rocker mechanism where ankle ROM is limited, improving lower limb function and reducing the mechanical burden on the ankle joint. The findings of this chapter support anecdotal clinical evidence at the Leeds CCC that patients using the modified footwear might experience reduced symptoms and improved HRQoL.

6.3 Limitation of current work

The specific limitations of this thesis have been presented in each chapter. In this section, therefore, the overarching limitations of this thesis design, methods and resulting outcomes are discussed.

The sample size in the prevalence study (Chapter Three) was small (n=157) owing to the requirement of the patient to have been compliant with the prophylaxis CFC treatment, reporting of treatment via Haemtrack, with concurrent full and electronic HJHS uploaded from each centre. At the time of data collection, the use of electronic recording was not universally adopted by UK haemophilia centres, nor were they uploaded as individual joint HJHS, therefore limiting the number of patients that were included in Chapter Three. It is expected that the number of patients would increase as centres adopt electronic methods of recording the HJHS rather than paper copies. The recent pandemic has also seen changes to how clinical data is collected and recorded, with more centres willing to adopt electronic methods of data reporting. Therefore if the study was undertaken today the sample size may be larger, and make the finding more generalisable to the haemophilia population.

The samples of haemophilia B patients in both Chapter Three (n=19), Chapter Four (n=34) and those with moderate haemophilia (n=29) in Chapter Four were small but an appropriate proportion of the cohort. Adequate recruitment of haemophilia B participants is an often reported limitation in the study of MSK complications of haemophilia, due to the low prevalence [5, 234]. The small sample size highlights the difficulty in obtaining adequate samples in rare diseases where small numbers are registered at each

haemophilia centre. Attempts were made in Chapter Four to increase patient numbers with 18 sites used for recruitment. Future studies may benefit from obtaining study data from people with haemophilia B and moderate haemophilia from a much wider sample with European and International collaboration to ascertain the true impact of disease type and severity. Reporting of MSK disease in haemophilia has been grouped in physical therapy and biomechanical studies [340, 341], however when examining the consequence of bleeding, joint health and HRQoL is different between haemophilia types [5, 235, 264]. AJBR are lower in people with haemophilia B with fewer complications but no definitive study has been undertaken to establish whether the proposed lower level of bleed prevalence, intensity and lower levels of joint haemarthropathy identified in part in this thesis is true.

Haemophilia is a lifelong condition characterised by bleeding within soft tissue and joints. Whilst the data reported in Chapter Three was obtained from a national haemophilia database the reported bleeding data and concurrent joint health using the HJHS was a relatively new addition to the database at the time of data reporting. Future prevalence studies would benefit from reporting of longitudinal bleed data and concurrent joint health to ascertain the bleeding profile and decline in joint health over time, but this was beyond the scope of this thesis.

Additional data related to treatment and trough levels were collected, but not included in the final report owing to incompleteness, inconsistencies in reporting and different methods of obtaining trough levels such as length of time without treatment and reporting methods. Obtaining trough data would have significantly strengthened treatment findings, but the primary outcome of this study (HRQoL and foot and ankle PROMs) were to target (n=255/245) with 243 suitable for analysis and the primary outcome unaffected.

In the mechanistic study reported in Chapter Five, some carryover effects between footwear conditions may have affected some of the specific biomechanical parameters reported. The carryover effect may have occurred due to an inadequate washout period

between conditions. When testing a footwear intervention there should be an adequate period of time between wearing different conditions [313]. A five minute washout period was used between conditions, which may not have been adequate. The effect was only observed in a small number of outcomes but attempts should be made in future studies to mitigate carryover where a Williams design is not possible [127].

The kinetic and kinematic parameters of gait were only captured during the stance phase in Chapter Five. Whilst this did not affect the study design, assessment during the swing phase would provide further detail on the effect of the LASER intervention and individual footwear components on the unloaded limb [91]. In the presence of multi-joint haemarthropathy the resultant muscle atrophy, restrictions in ROM and the additional weight of the LASER intervention may be detrimental to lower limb biomechanical parameters [135]. The use of a single segment foot model to capture in boot kinetic and kinematic data may be perceived as limited, owing to the complexities of the foot [111]. Multi-segment foot modelling is preferred when evaluating the complex kinematics of the foot, however, a single segment was used to model the ankle kinetics as well as the kinematics. This pragmatic approach was taken as ankle kinetics are mostly modelled as a single segment (foot, shank), and biomechanical outcomes were specific to the ankle, therefore a multi-segment model would be less necessary. In addition Chapter Five sought to understand the mechanical effect of the LASER intervention and cutting multiple holes in footwear to accommodate a multi-segment model may have decreased boot integrity, a potential source of bias in data collection [20].

Limitations of the statistical approach used to analyse biomechanical data are acknowledged. Repeated gait measures adopted to test differences between footwear conditions typically incorporate error or “variation” in biomechanical outcomes [342]. Understanding the magnitude of error, minimally important differences of results and minimal levels of detectable change may support the interpretation of data in a target population such as those patients with ankle haemarthropathy. Gait analysis used in this thesis examined data from discrete-time point(s) to test the hypothesis however

comparisons are limited to peak values for the gait cycle [111]. Analysis over the entirety of the gait cycle using methods such as Statistical Parametric Mapping (SPM) has been introduced recently to provide an insight into function over the course of a time series and detect to timing and magnitude of differences providing a more pragmatic approach to biomechanical analysis [329, 330]. Whist the use of SPM was not within the scope of this thesis, owing to the proposed footwear mechanisms of change and large dataset, future research in haemophilia and pathological gait may provide further insight.

6.4 Directions of future research

The research undertaken in this thesis and the direction of future research has been identified in the preceding chapters. Therefore an overview and further clarification are presented here.

Evaluation of the true ankle haemarthrosis and concurrent haemarthropathy require large longitudinal studies of bleed history and treatment regimes in those deemed compliant with treatment. Detailed evaluations of patients who fall below the UKHCDO threshold of 75% reporting compliance are also required to obtain the true UK prevalence and incidence of ankle joint haemarthrosis and joint disease. This may require a different approach to data collection with less focus on those most compliant with treatment and collation of longitudinal HJHS data from childhood through to adulthood, and into older adult population across UK haemophilia care. Future research designs could therefore obtain longitudinal data on the prevalence of patients who are compliant and non-compliant with haemophilia joint health scoring.

Further research is needed to establish the relationship between the incidence of ankle haemarthrosis and the point at which ankle haemarthropathy starts to affect HRQoL and foot and ankle PROMs. One major theme in the Chapter Four impact study was the significant amount of ankle haemarthropathy in those with moderate haemophilia, with comparable impact to severe haemophilia. Recommendations for future research would include closer monitoring of ankle joint haemarthrosis, incidence and development of

haemarthropathy in those with and without a history of bleeding, to understand the true incidence in the UK haemophilia population. Similarly, with the emergence of novel factor and non-factor treatment products such as EHL and bispecific monoclonal antibodies, there is a need to understand the non-pharmacological contribution of treatment to HRQoL and foot and ankle PROMs.

A mechanism of action study is next required in a cohort of haemophilia patients with ankle and multi-joint haemarthropathy to establish the safety and confirm mechanical effects of the LASER intervention in haemophilia cases before implementation in practice or inclusion as part of a complex intervention trial. The LASER intervention has the potential to reduce the burden of established ankle haemarthropathy, but also in early joint disease before biomechanical limitations and pain are yet to be established. The methods used in Chapter Five have produced a biomechanical protocol that may be allied to other intervention studies that aim to obtain the true effect within footwear. Therefore the novel biomechanical model may be applied to patients with ankle haemarthropathy and other diseases that affect the ankle joint.

6.5 Overview of findings

The aims of this thesis were as follows; firstly to identify the prevalence of ankle haemarthrosis and concurrent joint health in severe haemophilia A and B. The findings of Chapter Four identified the prevalence of ankle haemarthropathy is similar to other commonly affected joints, however, the ankle is disproportionately affected by haemarthropathy. The second aim was to provide insight into the impact of ankle haemarthropathy on HRQoL and foot and ankle specific PROMs. The finds of Chapter Five have identified that patients with ankle haemarthropathy have poor HRQoL and foot and ankle specific outcomes which are driven by chronic pain. The final aim was to investigate the mechanism of action of the LASER intervention. Chapter Five has established that the LASER intervention reduces the kinetic and kinematics effect at the ankle whilst minimising the proximal effect at the knee and hip.

6.6 Conclusion

Ankle haemarthrosis and the resultant haemarthropathy is a significant burden to patients with moderate and severe haemophilia. In patients with severe non-inhibitor haemophilia who adhered to prophylaxis, haemarthrosis still occurs, with disproportionate levels of haemarthropathy reported at the ankle. HRQoL and foot and ankle outcomes are severely affected with, poor outcomes reported in those with moderate to severe levels of ankle haemarthropathy. The driver for the decline in pain and whilst patients identify high levels of chronic ankle pain, treatment is sub-optimal in the use of pharmacological pain medication and non-pharmacological interventions. Therapeutically useful footwear and FFO are used by only a small proportion of patients identified in this thesis but do appear to be able to reduce the mechanical burden at the ankle joint. It remains to be shown definitively whether the use of footwear and FFO have a positive effect on patient-reported outcomes. The use of the LASER intervention has been investigated and reduces the biomechanical demands on the ankle joint with minimal proximal effect at the knee and hip, minimising the risk of subsequent haemarthrosis at these proximal structures. In future trials of targeted treatments for ankle haemarthropathy, the LASER intervention has potential as a therapeutic intervention.

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Appendix 1: HAPII patient questionnaire

UNIVERSITY OF LEEDS

HAPII Impact and prevalence study

Impact of blood induced ankle arthritis in haemophilia A and B questionnaire

Please complete the following questionnaire by answering all questions in Section A

A member of your care team will complete section B

If you have any questions please ask a member of your care team, or if you have taken home please call Richard Wilkins on 0113 3924939

Corresponding documentation

HAPII_protocol_v1.2
HAPII_PIS_v1.3
HAPII_consent_v1.3

Haemophilia Centre

Pt ID No

Thank you for taking part in this study. Please answer the following questions about your haemophilia and ankle arthritis

Please tick the box that applies to you or provide details

What is the month and year of birth?	Month		Year	
What type of haemophilia do you have?	A	Tick	B	Tick
Do you have moderate or severe Haemophilia?	Moderate	Tick	Severe	Tick
Do you treat with prophylaxis or on demand?	Prophylaxis	Tick	On-demand	Tick
If your treatment is by prophylaxis how often do you take your factor?	Daily	Tick	Every other day	Tick
	Other (please describe)			
If on-demand how often do you take factor? (Tick one)	Two times per week	Tick	Once per week	Tick
	Other (please describe)			
What dose of factor do take for your regular treatment?	UI			
If you have a "bleed" how much factor do you take per day?	UI			
On average how many days do you treat for following a MILD bleed?	Days			
On average how many days do you treat for following a SEVERE bleed?	Days			
How would you describe a bleed into a joint?				
Do you take regular pain medication for your joint pain?	Yes	Tick	No	Tick
	Medication:			
Do you have an inhibitor?	Yes	Tick	No	Tick

Do you have any target joints?	Yes	Tick	No	Tick
If yes which joints (please tick all that apply)	**Left**		**Right**	
	Shoulder	Tick	Shoulder	Tick
	Elbow	Tick	Elbow	Tick
	Wrist	Tick	Wrist	Tick
	Hip	Tick	Hip	Tick
	Knee	Tick	Knee	Tick
	Ankle	Tick	Ankle	Tick
How many ankle bleeds do you think you have had in the past 12 months	Number of bleeds LEFT ankle		Number of bleeds RIGHT ankle	
Do you have access to a physiotherapist?	Yes	Tick	No	Tick
Do you access to a podiatrist / chiropodist?	Yes	Tick	No	Tick
Does your podiatrist supply insoles?	Yes	Tick	No	Tick
Does your podiatrist / chiropodist provide routine treatment such as nail cutting or callus removal?	Yes	Tick	No	Tick
Do you wear hospital or specially adapted shoes?	Yes	Tick	No	Tick
Do you wear insoles in your footwear?	Yes	Tick	No	Tick
If yes, which type of insole do you have?	Shop brought	Tick	NHS supplied	Tick
	Private podiatrist	Tick		
Have you had any surgery to your ankles or feet?	Yes		No	
If yes, which ankle or foot	Left		Right	

Haemophilia Quality of life for Adults Questionnaire

The first set of questions asks about how **haemophilia** affects your **day-to-day activities**. Think about the **past 4 weeks** when answering these questions.

Please circle the best answer:

		None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
1.	Loss of joint mobility affects how I walk	0	1	2	3	4	5
2.	It is hard for me to climb the stairs	0	1	2	3	4	5
3.	It is *easy* for me to perform daily activities	0	1	2	3	4	5
4.	I am unable to leave the house because of my haemophilia	0	1	2	3	4	5
5.	I have to adjust my activities because of pain	0	1	2	3	4	5
6.	I am *able* to complete household tasks	0	1	2	3	4	5
7.	It is *easy* for me to lift heavy objects	0	1	2	3	4	5
8.	I depend on others to carry out activities around the home	0	1	2	3	4	5
9.	I am *able* to participate in sports	0	1	2	3	4	5
10.	I have difficulty travelling because of my haemophilia	0	1	2	3	4	5
11.	I am afraid of being far from a health care centre with emergency care facilities	0	1	2	3	4	5

The next set of questions asks about how **haemophilia** affects your **mood and feelings**. Think about the **past 4 weeks** when answering these questions.
Please circle the best answer:

		None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
12.	I am hopeful about the future	0	1	2	3	4	5
13.	I worry about accidents	0	1	2	3	4	5
14.	I am afraid of being hit or bumped	0	1	2	3	4	5
15.	I feel less confident than others	0	1	2	3	4	5
16.	I enjoy life	0	1	2	3	4	5
17.	I feel much older than my years	0	1	2	3	4	5
18.	I am afraid of internal bleeding	0	1	2	3	4	5
19.	I am in control of my life	0	1	2	3	4	5
20.	I feel like I'm taking a risk when I do things	0	1	2	3	4	5
21.	I feel frustrated because I can't do what I want to do	0	1	2	3	4	5
22.	Because of my haemophilia, I have difficulty planning for the future	0	1	2	3	4	5

Now we would like to ask you about how **haemophilia** affects your **work or school life**, **family life and social life**. Think about the **past 4 weeks** when answering these questions.

Please circle the best answer:

		None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
23.	I worry about finding or losing a job	0	1	2	3	4	5
24.	I worry about missing work or school because of my haemophilia	0	1	2	3	4	5
25.	I experience restrictions at work or school	0	1	2	3	4	5
26.	I feel like a burden to my family	0	1	2	3	4	5
27.	I worry about having children	0	1	2	3	4	5
28.	Haemophilia interferes with my relationships with my friends	0	1	2	3	4	5
29.	I worry about not being able to provide for my family	0	1	2	3	4	5
30.	I am afraid to go to crowded places like concerts or bars for fear of being bumped or injured	0	1	2	3	4	5
31.	I feel different from others because of my haemophilia	0	1	2	3	4	5
32.	I feel I have the same opportunities to succeed in life as others	0	1	2	3	4	5
33.	Others treat me differently	0	1	2	3	4	5
34.	I feel I can carry out a normal life like the rest of society	0	1	2	3	4	5
35.	Haemophilia interferes with my ability to have an intimate relationship with another person	0	1	2	3	4	5
36.	I am afraid of having a bleed in public	0	1	2	3	4	5

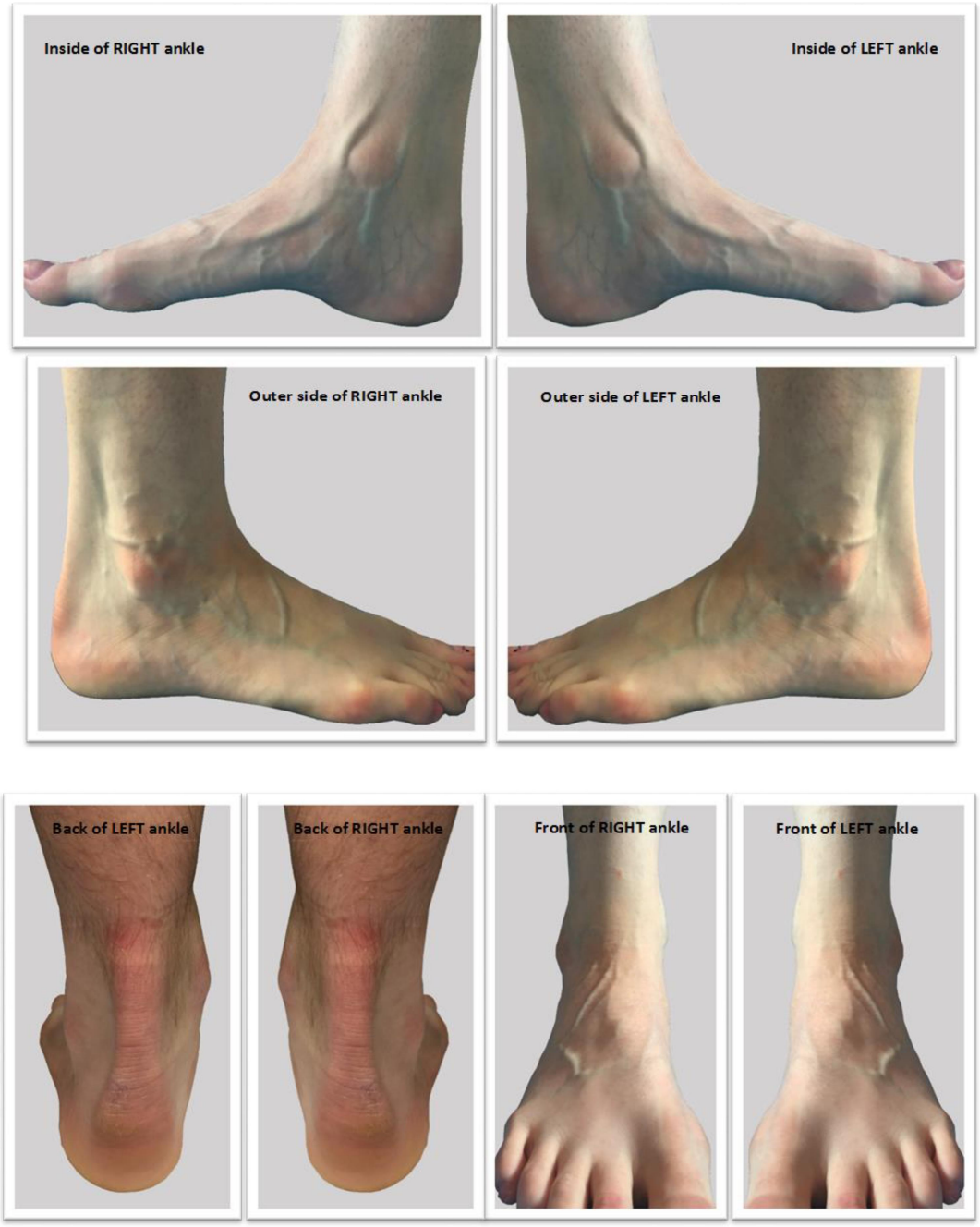
The following questions ask about your experiences with your **haemophilia treatment**. Think about the **past 4 weeks** when answering these questions.

Please circle the best answer:

		None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
37.	My haemophilia treatment interferes with my daily activities	0	1	2	3	4	5
38.	My infusions for haemophilia are stressful	0	1	2	3	4	5
39.	I worry about the safety of my treatment	0	1	2	3	4	5
40.	I worry about being treated by health care providers who do not know how to treat haemophilia	0	1	2	3	4	5
41.	I worry about the availability of haemophilia products	0	1	2	3	4	5

Have you experienced foot pain lasting at least one day during the past month? On the foot and ankle diagrams below please shade in areas where you have experienced pain.

If you have multiple areas of pain please draw an **arrow** that points to the most painful site



Pain in your ankle over the last six months

How painful has your ankle been over the past six months?

No Pain	0	1	2	3	4	5	6	7	8	9	10	***Pain as bad as you can imagine***

Please think about your ankles after an acute bleed

How much pain do you have in your ankle straight after a bleed?

No Pain	0	1	2	3	4	5	6	7	8	9	10	***Pain as bad as you can imagine***

Think about factor use when you have had a mild bleed?

You have had a **mild** bleed and treated it with factor. How much improvement do you have in pain after your usual extra treatment period?

Very much improved	Much improved	Minimally improved	No change	Minimally worse	Much worse	Very much worse

Think about factor use when you have had a severe bleed?

You have had a **severe** bleed and treated it with factor. How much improvement do you have in pain after your usual extra treatment period?

Very much improved	Much improved	Minimally improved	No change	Minimally worse	Much worse	Very much worse

Manchester-Oxford Foot Questionnaire (MOxFQ)

English version for the United Kingdom

Prior to completing the Questionnaire please complete the following:-

Today's Date:

				2	0		
D	D	M	M	Y	Y	Y	Y

On which side of your body is the affected joint, **for which you are receiving/have received treatment**.

Left ❑

Right ❑

Both ❑

If you said 'both', please complete the <u>first</u> questionnaire thinking about the <u>right side</u>. A second questionnaire, for the left side, will follow.

Circle as appropriate **Right / Left** Please tick (✓) one box for each statement.

1. **During the past 4 weeks this has applied to me:**

I have pain in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

2. **During the past 4 weeks this has applied to me:**

I avoid walking long distances because of pain in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

3. **During the past 4 weeks this has applied to me:**

I change the way I walk due to pain in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

4. **During the past 4 weeks this has applied to me:**

I walk slowly because of pain in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

5. **During the past 4 weeks this has applied to me:**

I have to stop and rest my foot/ankle because of pain

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

6. **During the past 4 weeks this has applied to me:**

I avoid some hard or rough surfaces because of pain in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

7. During the past 4 weeks this has applied to me:

I avoid standing for a long time because of pain in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

8. During the past 4 weeks this has applied to me:

I catch the bus or use the car instead of walking, because of pain in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

9. During the past 4 weeks this has applied to me:

I feel self-conscious about my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

10. During the past 4 weeks this has applied to me:

I feel self-conscious about the shoes I have to wear

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

11. During the past 4 weeks this has applied to me:

The pain in my foot/ankle is more painful in the evening

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

12. During the past 4 weeks this has applied to me:

I get shooting pains in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

13. During the past 4 weeks this has applied to me:

The pain in my foot/ankle prevents me from carrying out my work/everyday activities

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

14. During the past 4 weeks this has applied to me:

I am unable to do all my social or recreational activities because of pain in my foot/ankle

None of the time	Rarely	Some of the time	Most of the time	All of the time
☐	☐	☐	☐	☐

15. During the past 4 weeks...

How would you describe the pain you usually have in your foot/ankle?

None	Very mild	Mild	Moderate	Severe
☐	☐	☐	☐	☐

16. During the past 4 weeks...

Have you been troubled by pain from your foot/ankle in bed at night?

No nights	Only 1 or 2 nights	Some nights	Most nights	Every night
☐	☐	☐	☐	☐

Finally, please check that you have answered every question.

Thank you very much.

Thank you for completing the questionnaire. Once the study is finished you will receive details of the outcome

To be completed by Consultant, nurse or AHP

Section B:

What is the participants height	Cm					
What is the participants weight	Kg					
What is the participants baseline factor level	UI					
How long has the participant been on prophylaxis (*estimate)	years					
What is the participant's trough level on prophylaxis	UI					
Has the participant's product/ regime changed in the last 12 months						
What is the participant's target joint(s)						
Does the participant use haemtrack?	yes	Tick		no	Tick	
How many joint bleeds has the participant had in the past 12 months?						
What product does the participant use						
Haemophilia Joint Health Score (HJHS)	Left Ankle			Right Ankle		
Is there imaging evidence of blood induced ankle arthritis	Yes			No		
If yes which imaging modality was used to confirm	MRI		X-ray		US	
Please provide details of any ankle or foot surgery Please provide details of procedure and date	Left			Right		

Appendix 2: Patient pain pilot questionnaire

Participant No		

Please rank the following questions 1 to 3 (1= best 3= worse)

We are developing a questionnaire to best capture the impact of ankle problems on your life. These are usually completed using a scale from 0-10, or a measurement of improvement as provided below. You can help by telling us which of the three questions would be the most relevant for you in capturing the effect/impact of any ankle problems.

Pain in your ankle over the last six months

How much pain have you had in general in your ankles over the past six months? ☐

How painful has your ankle been over the past six months? ☐

On average how much pain has your ankle caused pain over the past six month? ☐

No Pain	0	1	2	3	4	5	6	7	8	9	10	***Pain as bad as you can imagine***

Please think about your ankles after an acute bleed

How much pain would you have in your ankle immediately following a bleed? ☐

How much pain do you have in your ankle straight after a bleed? ☐

Thinking about pain, how much pain does a bleed into your ankle cause to you? ☐

No Pain	0	1	2	3	4	5	6	7	8	9	10	***Pain as bad as you can imagine***

Think about factor use when you have had a bleed?

Following your usual treatment for an acute episode of bleeding how much improvement do you have in pain immediately following your usual treatment regime? ☐

When you have treated the symptoms of a bleed with factor how much improvement in pain do you experience after your usual extra treatment? ☐

You have had a bleed and treated it with factor. How much improvement do you have in pain after your usual extra treatment period? ☐

HAPII Consultant survey

Page 1: Version 1.1 Date 10/05/2019 IRAS code 206141

We aim to take a snap shot of services for the management of people with chronic haemarthrosis affecting the ankle at haemophilia centres across the United Kingdom.

This short survey will be anonymised and only identifiable by haemophilia centre for comparison by regions.

By completion and submission of this survey you give consent for data to be used as part of a study titled Prevalence and impact of blood induced ankle arthritis in people with haemophilia A and B, The HAPII study IRAS code 206141.

If you require any further information please contact Richard Wilkins NIHR clinical doctoral research fellow at **r.a.wilkins@leeds.ac.uk**

1. At which haemophilia centre do you currently work? ✱ *Required*

Your answer should be no more than 20 characters long.

1.a. Is your centre a comprehensive care centre (CCC) or haemophilia treatment centre (HTC) ✱ *Required*

2. Do your patients have access to physiotherapy services? ✱ *Required*

- Yes - direct referral within haemophilia centre care team

1 / 5

- Yes - direct referral outside of haemophilia centre care team
- Yes - indirect referral e.g. GP
- Yes - indirect referral e.g. other CCC
- No access

3. Do your patients have access to orthotist services for footwear, ankle braces etc? ✱ *Required*

- Yes - direct referral within haemophilia centre care team
- Yes - direct referral outside of haemophilia centre care team
- Yes - indirect referral, e.g. via GP
- Yes - indirect referral e.g. other CCC
- No access

4. Do your patients have access to a podiatrist for a musculoskeletal assessment and provision of foot orthoses/ insoles? ✱ *Required*

- Yes - direct referral within of haemophilia centre care team
- Yes - direct referral outside of haemophilia centre care team
- Yes - indirect referral e.g. via GP
- Yes - indirect referral e.g. other CCC
- No access

5. Do your patients have access to podiatry services for routine foot care (nail care, callus, corns etc.)? ✱ *Required*

- Yes - direct referral within haemophilia centre care team

- Yes - direct referral outside of haemophilia centre care team
- Yes - indirect referral e.g. via GP
- Yes - indirect referral e.g. other CCC
- No access

6. Do your patients have access to psychology services? ✱ *Required*

- Yes - direct referral within haemophilia centre care team
- Yes - direct referral outside of haemophilia centre care team
- Yes - indirect referral e.g. via GP
- Yes - indirect referral e.g. other CCC
- No access

7. Do your patients have access to orthopaedic (foot & ankle) surgery services? ✱ *Required*

- Yes - direct referral within haemophilia centre care team
- Yes - direct referral outside of haemophilia centre care team
- Yes - indirect referral e.g. via GP
- Yes - indirect referral e.g. other CCC
- No access

8. Do your patients have access to rheumatology services? ✱ *Required*

- Yes - direct referral within haemophilia centre care team
- Yes - direct referral outside of haemophilia centre care team
- Yes - indirect referral e.g. via GP

- Yes - indirect referral e.g. other CCC
- No access

9. Do your patients have access to point of care diagnostic ultrasound services? * *Required*

- Yes - direct referral within haemophilia centre care team
- Yes - direct referral outside of haemophilia centre care team
- Yes - indirect referral e.g. via GP
- Yes - indirect referral e.g. other CCC
- No access

10. Do your patients have access to a radioactive synovectomy service? * *Required*

- Yes - direct referral within haemophilia centre care team
- Yes - direct referral outside of haemophilia centre care team
- Yes - indirect referral e.g. via GP
- Yes - indirect referral e.g. other CCC
- No access

Page 2: HAPII study IRAS ID 206141

Thankyou for participating in the HAPII consultant questionaire. If you require any futher information please contact Richard Wilkins at **r.a.wilkins@leeds.ac.uk**

Key for selection options

1.a - Is your centre a comprehensive care centre (CCC) or haemophilia treatment centre (HTC)

CCC
HTC
