

**The Influence of Non-Haematological Factors on the Development
of Ankle Arthropathy in Haemophilia**

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of Brighton for the degree of Doctor of Philosophy.

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Abstract: The Influence of Non-Haematological Factors on the Development of Ankle Arthropathy in Haemophilia

Introduction. Haemophilia is an inherited condition in which circulating blood clotting factors are much reduced or absent resulting in the tendency to bleed into joint cavities where the ankle is the most commonly affected. Prophylactic replacement of clotting factors has much improved joint health in the majority of people with haemophilia however many continue to develop joint disease.

Purpose. To explore the potential for non-haematological factors to influence the development of haemophilic arthropathy at the ankle.

Methods. This study had two phases. Factors for investigation were determined using a Delphi process and subsequently preliminary clinical instrument testing occurred. Finally a case-control correlational study was carried out to investigate the presence of selected factors in a haemophilia cohort compared with normal volunteers.

Results. Forty-two factors reached consensus from the Delphi Process of which 22 were selected for onward investigation comprising musculoskeletal, exercise, and haematological factors. In a case-control study with 90 participants, six factors successfully differentiated the Haemophilia Ankle group from the others. A further three factors separated people with haemophilia from normal volunteers representing musculoskeletal differences that cannot be attributed to arthropathy. A regression model was developed comprising: the Ankle Lunge Test, Foot and Ankle Ability Measure (FAAM), Duration of Exposure to a key sport and Subtalar joint inversion which correctly predicted 89.7% of cases with 86.7% sensitivity and 92.9% specificity.

Conclusions. These results represent the first attempt to understand the interaction of factors that influence the arthropathy development. The FAAM sports subscale and Duration of Exposure to a key sport were identified as independent variables with the strongest association with haemophilic arthropathy at the ankle. Avenues for physiotherapeutic intervention have been identified with preventative screening tools and pre-habilitation programmes possible for young boys with haemophilia at risk of developing this debilitating condition.

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Abbreviations

Activities of daily living	ADL
Analysis of variance	ANOVA
Ankle joint complex	AJC
Ankle lunge test	ALT
Anterior cruciate ligament	ACL
Articular cartilage	AC
Benninghof Structure	BS
Body mass index	BMI
Cardiovascular	CV
Centimetres	Cm
Centre of mass	COM
Chief investigator	CI
Chronic ankle instability	CAI
Cumberland ankle instability tool	CAIT
Deoxyribonucleic acid	DNA
Dependent variable	DV
Dorsiflexion	DF
Electronic Appendix	e-Appendix
Electromyography	EMG
Extracellular matrix	ECM
Factor IX	FIX
Factor VIII	FVIII
Flexor hallucis longus	FHL
Foot and ankle ability measure	FAAM
Gluteus maximus	GMx
Gluteus medius	GMd
Glycoaminoglycans	GAGs
Ground reaction force	GRF
Haemophilia Joint Health Score	HJHS
Haemophilia with ankle disease	HmAk
Haemophilia with no joint disease	HmC
Haemophilic arthropathy	HA
Horizontal ground reaction force	hGRF
Human activity profile	HAP
Independent variable	IV
Interleukin	IL
Katharine Dormandy Haemophilia and Thrombosis Centre	KDHC
Kilograms	Kg
Lateral ankle sprain	LAS
Magnetic resonance imaging	MRI
Maximum voluntary isometric contraction	MVIC
Metatarsophalangeal joint	MTPJ
Minimally clinical important difference	MCID

Mixed methods research	MMR
Moving average	MAV
Musculoskeletal	MSK
National Health Service	NHS
National Institute for Health Research	NIHR
Normal volunteers	NV
Osteoarthritis	OA
Person/People with haemophilia	PWH
Plantarflexion	PF
Principal Investigator	PI
Principle component analysis	PCA
Randomised controlled trial	RCT
Range of movement	ROM
Real World Research	RWR
Receiver operating characteristic	ROC
Research Team	RT
Rheumatoid arthritis	RA
Single leg squat test	SLSq
Standard deviation	SD
Standard Operating Procedures	SOP
Star excursion balance test	SEBT
Surface electromyography	sEMG
Surface Electromyography for the Non-Invasive Assessment of Muscles	SENIAM
Timed single leg stance	TSLS
Tumour necrosing factor	TNF
United Kingdom	UK
Unites States of America	USA
Vertical ground reaction force	vGRF
Visual analogue scale	VAS

Chapter 1 Introduction to Haemophilia and Haemophilic Arthropathy

1.1 Introduction

Haemophilia A and B are X-linked inherited bleeding disorders characterised by reduction or absence of circulating factor VIII (FVIII) and IX (FIX) respectively leading to an inability to form an effective clot. Joint arthropathy secondary to recurrent bleeds is the most disabling complication in persons with haemophilia (PWH) and despite the advances made in the haematological management, the haemophilia community's goal of no or minimal joint damage is yet to be realised. This goal is complicated by the varying clinical presentations of PWH who have similar disease profiles. There is an experiential belief that the development of haemophilic arthropathy (HA) is multifactorial potentially encompassing non-haematological mechanisms. However this is not reflected in published research and has not been well studied; a need exists for further research into the pathogenesis of HA.

1.2 Research Journey and Evolution of the Study

Approximately 13 years ago as a new musculoskeletal (MSK) clinical lead physiotherapist with an interest in lower limb biomechanics I was asked for input on several cases by the haemophilia service clinical specialist physiotherapist. I had no previous exposure to this condition and I was quite taken aback by the level of disability present in some young patients. As with many areas of physiotherapy practice there was little evidence associated with the management of HA. Given my own area of special interest, I was particularly surprised to find that it was standard practice for all the boys to be provided with a rigid in-shoe orthotic and that good evidence for the practice was absent.

There were certainly a percentage of boys who had developmental abnormalities in their ankle joints secondary to joint bleeds interfering with the growing epiphysis, however others were just experiencing the transient changes to foot posture that occur secondary to growth spurts. With continued exposure to the condition, the clinical specialist physiotherapist and I discussed many musculoskeletal issues occurring secondary to the haemophilia and in particular, the idea that presenting gait abnormalities were leading to alteration in joint loading and thereby affecting bleeding rates. We realised that these theories and ideas would benefit from formalisation and investigation.

A research project around experimental exploration of gait was planned but pregnancy of my colleague prevented the completion of this. However, I continued to discuss my thoughts about joint disease with other centre clinicians including the new clinical specialist. This resulted in my co-supervision of a Masters-level research project: The effect of neutral-cushioned running shoes on the intra-articular force in the haemophilic ankle (McLaughlin et al., 2010). This study produced some interesting results but I felt that it was jumping into the middle of the problem instead of building evidence from first principles.

Around this time, physiotherapy-driven MSK research was rising in profile in the haemophilia community in terms of high quality research publishing in the area of gait analysis (Lobet et al., 2011). Co-operation in the haemophilia community is largely good with a bi-annual musculoskeletal conference provided by the World Federation of Haemophilia and also an annual study day in the UK. This allowed me to "bounce" my ideas around and to find that many were thinking along the same lines. Support within the Katharine Dormandy Haemophilia Centre provided me with the opportunity to formally begin to investigate my theories.

As a clinician, I felt that I was seeing the sequelae of the haemophilia rather than the condition itself and viewed these consequences as the MSK issues that they are. I therefore felt that taking an alternate perspective by not placing the haematology in the centre of theory generation might illuminate the differences present within each PWH when considering the development of HA. After several years of discussion and providing opinion on cases I had noted the presence of certain signs such as joint hypermobility, poor balance and poor control of movement. I felt particularly strongly about these cases due to the young age that the joint disease begins to become debilitating and this even more so for those not fortunate enough to be born in a country with a good health care system.

Attendance at the MSK haemophilia conferences was enlightening but I noted an undercurrent from some clinicians that the bleeding was all that mattered: the blood in the joint was the only problem. If that were true, then all articular exposures to blood should result in a HA-type presentation. To me, there should be no HA development if stresses to the joint tissues could be limited further, both in terms of limiting bleeding, and avoiding further impact on already vulnerable joints. It also seemed logical that the source/s of these extra stresses were unlikely to be haematological in origin. I decided to focus on the ankle joint as it was the most commonly affected and was already an area of interest to me.

From the initial premise of assessing the effects of gait changes on HA development, the ideas and scope of the study grew, outstripping the capacity of a single thesis, and so a research programme was developed in which this thesis plays a central role with investigation continuing after the completion of the doctoral process. Support for the research programme was gained from the

Private Physiotherapy Education Fund and Pfizer Limited's Investigator-Initiated Research grant programme.

This chapter introduces the reader to the crux of the thesis by describing haemophilia, its management, and HA. The potential impact of the research programme is described and finally the thesis is outlined.

1.3 Haemophilia

Prevalence of haemophilia A is 1 in 5000 live births and represents 80% of cases (Josephson, 2013). Haemophilia is classified depending on the severity of the factor deficiency so that circulating factor levels of less than 1% is considered severe, 1-5% moderate and over 5% but less than normal, mild (at least 25% is required for normal haemostasis) (White et al., 2001). Bleeding into the joints is the most common expression of severe haemophilia but bleeds can occur into muscles, other soft tissues, gastrointestinal tract and central nervous system. In those with a moderate presentation bleeding typically occurs in response to trauma but if tissue damage becomes chronic, bleeding is provoked more easily and in those with a mild presentation bleeding usually occurs in response to major tissue damage or trauma, or surgery (Josephson, 2013).

In a severe presentation, the pattern of bleeding into the joints varies from person to person and it can also shift from joint to joint. As the person ages, the frequency of bleeding is known to decrease below that experienced in childhood and adolescence sometimes leaving behind functional joints (Mulder & Llinas, 2004). However, within the classification based on residual circulating factor levels, there are anomalies. These include:

- A severe classification presenting with a mild bleeding profile, reported in 10 - 15% of severe cases (Aznar et al., 2000).
- A moderate classification presenting with a severe bleeding profile (Den

Uijl et al., 2009).

- The expression of the FVIII/FIX genotype, the main determinant of the amount of circulating factor level and so disease severity, not fully characterising the bleeding presentation (Santagostino et al., 2010).
- People with mild and moderate presentations developing HA at the ankle (Ling et al., 2011).

The reasons for the heterogeneous presentation of haemophilia remain unclear (Santagostino, et al., 2010). This complicates the medical management. The researcher contends that non-haematological factors might contribute to this variability in presentation but very little is known about these factors.

1.4 Haemophilia Management

The management of haemophilia is dependent on both the severity of the disease and the severity of the presentation. In severe presentations primary treatment consists of replacing the missing coagulation factors either episodically on-demand in response to acute bleeds or prophylactically in order to prevent them and thereby limit joint damage. The development of prophylaxis as a protocol occurred in response to the observation that moderate PWH did not tend to develop severe joint disease. The initial regimens were begun in Sweden (Nilsson, Blombäck, & Ahlberg, 1970), and have become the standard of care in most countries whose health care systems will support it, however evidence of its efficacy has only been reported recently via longitudinal study of prophylaxis versus episodic regimens (Gringeri et al., 2011; Manco-Johnson, 2007; Valentino, Mamonov, et al., 2012). These studies indicate that orthopaedic joint outcomes are improved with early introduction of a prophylaxis regime, ideally by the age of three (Valentino, Mamonov, et al., 2012). This is known as primary prophylaxis. As prophylaxis regimes usually require infusion

of factor concentrate 2 - 3 times per week, most PWH or their families learn to deliver the treatment at home. For young children indwelling central venous access is required which can be unpleasant for the child with a risk of infection (Dunn, 2005). Optimal cost effective dosing in these regimens remains unclear and is likely to remain so due to difficulties instituting large scale studies when the condition is rare and differing economic situations around the world preclude equal access to factor replacement (Josephson, 2013). Prophylaxis continues into adulthood and how long to persist with it given the natural reduction in number of bleeds with aging is unknown. Adults are sometimes started on (secondary) prophylaxis having presented with already established joint disease resulting in reduced arthropathy progression, and in the number and severity of joint bleeds (Collins, 2010; Den Uijl et al., 2014; Manco-Johnson, 2007).

The range of clinical presentations in moderate haemophilia is wide. In one self-reported study of 176 moderate PWH, 49% reported joint bleeds in the previous year and 27% reported some joint impairment. It has been suggested that these people may be under-treated due to lack of home treatment and less experience with bleed recognition (Den Uijl, et al., 2009). Twenty-five to thirty percent have need for prophylaxis for at least some period to manage their symptoms (Den Uijl, et al., 2009; Josephson, 2013). It has been reported that a baseline factor level of less/equal 2IU/dl (international units per decilitre) plus a history of the first joint bleed before five years of age predicts a bleeding phenotype similar to severe haemophilia in presentation (Den Uijl, Mauser, et al., 2011). Prophylaxis is considered in these cases. It is interesting to note that in one study the median age for a moderate PWH to require prophylaxis was 14 years (Den Uijl, Mauser, et al., 2011). The researcher considers that this might be important as it may represent external contributory factors such as growth spurts and moving towards independent decision making. However for the

majority of those with mild and moderate presentations the focus of therapy is to ensure adequate haemostasis for trauma-related bleeding and for planned invasive procedures (Josephson, 2013).

The aim of prophylactic factor replacement therapy is to transform severe haemophilia into a moderate form (Den Uijl, et al., 2014). However, as discussed above, there is no guarantee that a moderate classification based on circulating factor levels will prevent continued bleeding. A factor level between 1 and 5% suffices to prevent the majority of bleeds in the majority of severe PWHs. Furthermore joint damage can be averted by keeping FVIII or FIX at around 15% at all times (Den Uijl, Fischer, et al., 2011), that is transform to a mild haemophilia presentation but this practice would be financially unfeasible. Tailoring of prophylactic regimens continues to be a challenge. Josephson (2013) cited a lack of understanding of differences in coagulability, underlying joint damage and patient activity levels as key to improving individualising treatment plans. Should a PWH continue to sustain bleeding into joints the potential clinical outcome is HA, an overview of which is given in the next section.

1.5 Haemophilic Arthropathy

If bleeding occurs repeatedly into a specific joint, it becomes known as a target joint. Many definitions of a target joint appear in the literature, examples are: more than three clinically determined bleeds into a single joint in a three month period (Blanchette et al., 2004) or more than four haemarthroses in a six-month period (Valentino, Mamonov, et al., 2012). Mulder and Llinas (2004) describe one in which there is insufficient time between bleeds for a joint to return to baseline health prior to another bleed occurring without specifying a number of bleeds. A joint, irrespective of whether it has been identified as a target, may go

on to develop HA (Josephson, 2013).

HA has been described as occurring in three stages (Knobe & Berntorp, 2011):

1. Acute haemarthrosis
2. Chronic synovitis
3. Degenerative arthritis

During an acute haemarthrosis, a diffuse haematoma forms within the synovium that eventually penetrates into the joint cavity (Gilbert, 2000). This initial bleeding is reabsorbed taking 3 - 4 weeks (Mulder & Llinas, 2004), but should there be recurrent bleeding into the joint before this is complete, the synovium can exceed its capacity to reabsorb the blood and its breakdown products, resulting in a persistent presence within the joint. In particular, the iron-rich molecule hemosiderin deposits throughout the synovium and is thought to cause synovial inflammation (Roosendaal et al., 1998). It is thought that this molecule is capable of promoting the release of pro-inflammatory substances which results in the second stage: haemophilic synovitis (Knobe & Berntorp, 2011). Increased synovitic vascularity and hypertrophy result in even greater numbers of inflammatory cells in the joint. It is proposed that the thickened tissue becomes impinged within the joint during movement causing further damage and bleeding (Mulder & Llinas, 2004). It is also proposed that some of the bleeding occurrences may be sub-clinical that is, not overtly recognisable as joint bleeds (Rodriguez-Merchan, 1997). Valentino et al. (2012) suggested that if the synovitis persists for six-months then the condition should be referred to as HA. With chronicity, synovitis is replaced by a more fibrotic scarred picture. Changes begin to occur in the articular cartilage which eventually shows signs of degeneration (Valentino, Mamonov, et al., 2012). The damage to the articular cartilage is thought to occur dually via direct exposure to the blood and via the pro-inflammatory mediators (Jansen, Roosendaal, & Lefeber, 2008). The joint

loses range and associated muscle function becomes unreliable. The intra-articular changes can progress until the joint is obliterated. Haemophilic synovitis is most common between 6 – 16 years of age and the symptoms of HA commonly develop by the second or third decade of life (Rodriguez-Merchan, 1997). Figure 1.1 shows examples of magnetic resonance images (MRI) of normal and severe HA ankle joints.

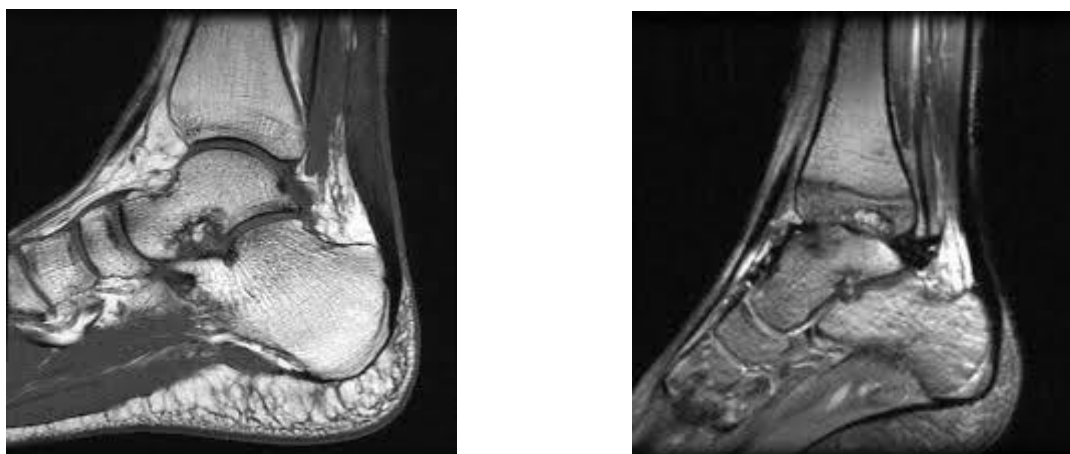


Figure 1-1 Normal (left) and advanced haemophilic arthropathy (right) ankle MRIs (Source: anonymised MRI scans courtesy of Dr Mary Mathias, Great Ormond Street Hospital, London)

The difference between haemophilic and non-haemophilic arthropathies is the fact that in the latter the joint is in itself pathological, whereas in haemophilia the joint is basically healthy. This implies that if bleeding is limited early enough, the joint damage can be also limited (Mulder & Llinas, 2004). Currently, in the era of prophylaxis, the most affected joints are, in descending order, the ankles, knees and elbows (Stephensen, Tait, et al., 2009). There are no conclusive theories as to why these joints are mainly affected but it is suggested that their being hinge joints may be a factor (Heijnen, Roosendaal, & Heim, 1997).

Pain is a common symptom associated with HA. It is associated both with acute bleeding situations and with the development of HA when chronic pain states may develop. There has been little research into the independent management

of pain in haemophilia and in an acute bleed situation, pain is managed as part of the overall treatment approach as described in 1.6. Several review articles and evaluations of chronic pain in haemophilia have been published (e.g. (Holstein et al., 2012)). In a study of 78 adults with severe haemophilia, the ankle was the most frequently mentioned painful joint. Analysis of pain outcomes as determined by the McGill pain questionnaire were found to explain between 3 – 22% in self-perceived functional scores determined by the Haemophilia Activities List. However no significant association was found between pain and arthrographic evidence of joint degeneration (Van Genderen et al., 2006). It is also reported that pain is both under-recognised and under-treated (Wiktop et al., 2012). In an ideal situation, this would be remedied by the primary prevention of pain.

1.6 Haemophilic Arthropathy Management

This section will provide a broad overview of HA management.

HA is managed ideally by prevention of bleeding episodes via prophylactic treatment regimens as already described. In the United Kingdom (UK), severe PWH are reviewed on a six-monthly basis in a multi-disciplinary clinic to both monitor the efficacy of their prophylaxis and the health of their joints.

Additionally, the physiotherapist will measure joint health once each year using a haemophilia-specific scoring system for children and adults. When an acute bleed occurs, the PWH administers additional pre-agreed doses of factor replacement. The P.R.I.C.E. (protection, rest, ice, compression, elevation) protocol is recommended, although the use of compression is limited to when the joint has stopped bleeding. Temporary splinting for pain relief may be recommended and short periods of restricted use of the affected joint.

Physiotherapy rehabilitation is essential to address any residual reduction in

motion and weakness.

With chronicity, physiotherapy interventions attempt to maintain joint range and function, and also to more closely monitor adjacent joints for signs of increased load (and so risk of damage) due to changes in kinetic chain function. Medical adjuncts for when the condition becomes more chronic include analgesia, the use of cox-2 inhibitor anti-inflammatory medications and rarely corticosteroids. If the condition is recalcitrant, surgical options to arrest the synovitis may be attempted. Both synoviorthesis (destruction of the joint's synovium using radioactive or chemical substances) and synovectomy (open or arthroscopic) are carried out to arrest the inflammatory process. In cases where the condition has progressed further joint debridement, arthroplasty or fusion are options (Knobe & Berntorp, 2011).

Prevention or amelioration of this painful and debilitating condition has become a high priority and early detection is crucial. Valentino (2012) stated that by 25 years of age, 90% of persons with severe haemophilia develop chronic degenerative changes in at least one joint. Moreover, 75% of haemophilia A patients worldwide are unable to access treatment (Porada et al., 2011). It has been stated that without treatment, adolescents with severe haemophilia will experience painful, swollen joints with restricted motion and the concomitant reduction in quality of life (Knobe & Berntorp, 2011). Currently, joint health is monitored using the Haemophilia Joint Health Score (HJHS) which is fully validated in children (Hilliard et al., 2006) and is undergoing validation in adults (e.g. (Fischer & Kleijn, 2013)) and it is believed by UK practitioners to be useful adjunct to haemophilia care but that it may be less useful for those with very early or very advanced joint disease. In very early joint disease, it is known that early signs may be present in asymptomatic joints (Manco - Johnson et al.,

2007) and it has been suggested that a score above 6 indicates a joint problem (Feldman, 2011), implying that it is possible to register a score without a joint problem being present. Therefore, identification of alternative methods of detecting early joint disease with high clinical utility would prove beneficial.

As stated previously, with chronicity this condition can become painful and will impact function at the ankle through difficulties weight-bearing and so may impact greatly on daily life. Pain and its management has been identified as an issue of importance in haemophilia and it could be considered a natural area of research for a physiotherapist. However, the researcher's interest in HA was preventative rather than reactionary and so the focus of this study programme involved working with people with much earlier presentations before pain has become an on-going issue.

There are potential predictive risk factors associated with the bleeding phenotype for who will present clinically with more bleeding episodes and so in theory would be more at risk of developing joint damage. However, these factors do not appear to hold true for all people. There remain a host of unknowns such as the influence of factors external to the haemophilia. The researcher considered it essential to investigate the potential of other factors to influence this clinical presentation.

1.7 Potential Impact of Study

The potential impact of this study is multifaceted and includes developing an improved understanding of the pathogenesis of HA. It is hoped that tools may be identified that will help in the early HA identification. It will help to develop a screening process for children to put into place primary preventative measures such as specific exercise advice and pre-habilitation programmes. The results will begin the process of developing a profile for an arthropathy phenotype

within haemophilia. The results may assist in further tailoring factor replacement therapy by identifying more risk factors for a severe bleeding phenotype. Finally, it will also identify areas of further study that can assess the impact of interventions to continue to build a holistic approach to managing this potentially debilitating condition.

1.8 Outline of the Thesis

This thesis is divided into twelve chapters. In Chapter Two, a literature review of the pathogenesis of HA considering the current theories and looking at literature from clinical areas external to haemophilia for further support or clarification is presented. The development and behaviour of articular cartilage is discussed. Theoretical concepts potentially relating the pathogenesis of HA with osteoarthritis are discussed. The literature review continues in Chapter Three examining the ankle joint and why it might demonstrate such vulnerability to HA. Given the focus of gait in research evidence, an overview is given with the differences found in paediatric gait elaborated as HA will initiate in childhood. Potential pathogenesis factors are considered in light of the ankle joint and its biomechanics but also the pathomechanics of the very common lateral ankle sprain. The research questions are presented. The researcher's worldview with respect to this study programme is described in Chapter Four together with the rationale for the mixed methods approach and the overall methodology, including a breakdown of the phases and stages of the study. Chapter Five presents the first phase of the study: the use of a Delphi process to identify factors for investigation. Results are reviewed for feasibility in order to select factors from those suggested for onward study. Chapters Six to Nine outline the development of the study protocol for the main case-control correlational study of the thesis. The methods and procedures are described in Chapter Six, and

Chapter Seven provides the rationale and in-depth explanation of the chosen assessment battery. In Chapter Eight, the development of an exploratory historical activity and exercise questionnaire is reported. Finally, in Chapter Nine a preliminary study of the Star Excursion Balance Test (Olmsted et al., 2002) with regards to gluteal muscle activation is presented. The case-control correlational study results and findings are presented in Chapter Ten including a discussion of statistical approaches. These results and findings are discussed in Chapter Eleven in terms of the original research questions and finally Chapter Twelve presents conclusions, evaluation of the impact of the results and ideas for onward study.

Chapter 2 Articular Cartilage and Arthropathy in Haemophilia

2.1 Introduction

As suggested in Chapter 1, the exact pathogenesis of haemophilic arthropathy (HA) remains incomplete and research in the area is confined to the direct effects of blood on the tissues of the joint. It is the researcher's contention that the pathogenesis of HA is not unimodal, rather the researcher suggests that it is complex and multifactorial in origin. In order to support this contention, in this chapter, the direct-blood pathogenesis evidence is examined and the queries that are raised for the researcher are addressed. The paradox between experimental data and clinical outcomes are described and evidence from other disciplines is used to elucidate and build on the direct-blood theory.

The published literature was searched using Medline and Google Scholar initially in 2012 and again in 2016. Owing to the necessity of investigating several unrelated subject areas within the chapter, there was no intention that there would be a systematic review and so search terms were used pertinent to the subject areas. For instance for the topic of haemophilic arthropathy, the following were selected: (haemophil* OR hemophil*) AND (arthropath* OR "joint disease") AND (aetiolog* OR etiolo* OR pathogene*). Across the chapter, studies have been included that are experimental design, case series', cohort studies and reviews, and book sections have also been considered. Having identified key articles, their reference and citation lists were perused for further information sources. Searches were limited to the year 2000 onwards but older key articles were included and articles were written in English. Study quality was also examined for instance the duration of follow up in case series.

2.2 Synopsis of Haematological Pathogenesis Evidence

Research has indicated that there are two pathogenetic pathways in operation: synovial inflammation and articular cartilage (AC) degeneration giving HA aspects of both rheumatoid arthritis (RA) and osteoarthritis (OA) (Roosendaal, van Rinsum, et al., 1999; van Vulpen et al., 2016).

2.2.1 Synovial effects

Repeated bleeds into a joint without adequate time in between to allow for recovery will overwhelm the synovium's capacity for clearance. Several adaptations occur including synovial hypertrophy and neovascularisation. The iron-rich blood breakdown product haemosiderin deposits inside the joint (Roosendaal, et al., 1998) causing an inflammatory response stimulating proliferation of synoviocytes. The iron-laden synoviocytes produce pro-inflammatory cytokines, including interleukin (IL)-1 β , IL-6, and tumour necrosis factor alpha (TNF α) (Roosendaal, van Rinsum, et al., 1999; Roosendaal, et al., 1998).

The pathological synovial membrane has been observed to be irregular and villous and the neovascularisation that develops is friable. In mice the pathologic synovium induces an overexpression of the proto-oncogene c-myc, which is associated with synovial cell proliferation, and of the tumour suppressor binding protein mdm2, resulting in a suspension of synovial cell apoptosis (Hakobyan et al., 2004; Wen et al., 2002). These changes ultimately make the joint prone to further bleeding and potentially consequent degradative processes. As synovitis becomes chronic a small pannus at the AC margins may develop (van Vulpen, et al., 2016).

2.2.2 Cartilage degeneration

AC destruction is proposed to follow on from chronic synovitis but additionally from direct blood exposure. Firstly the pro-inflammatory cytokines and some proteases capable of extracellular matrix (ECM) destruction are released from the synovium (Hakobyan, Kazarian, & Valentino, 2005; Roosendaal, et al., 1998). It is suggested that destructive chemicals are released within 48 hours after a bleed and may cause prolonged damage (Jansen et al., 2009).

From the perspective of the effects of direct blood exposure, in vitro experimentation indicates that ECM turnover is accelerated and chondrocyte cells die off (Roosendaal et al., 1997). However, this study both called changes “practically irreversible” and also recorded the limit to their effects as 10 weeks. It has also been found that IL-1 β and TNF α produce transient effects on proteoglycan turnover (Hooiveld, Roosendaal, Van Den Berg, et al., 2003). It has been suggested that as chondrocyte proliferation is normally low any interruption to their function may have a long lasting effect on ECM health (van Vulpen, et al., 2016). It has further been suggested based on in vivo experiments with beagle dogs, that these changes are more likely to occur with immature AC (Hooiveld, Roosendaal, Vianen, et al., 2003).

This examination of the published evidence on the pathogenesis of HA by the researcher has led them to conclude that cause and effect has not been fully demonstrated. The researcher also has concerns regarding the generalisability of results. Concerns are induced on two fronts: that the results may not be supportable due to methods used, and that due to the studies being reductive in design and only considering biochemistry, other key factors are not taken into account leading to potential misinterpretation of results. These concerns are summarised as follows:

- The biochemical model suggested in the literature reviewed so far does not fully does not correlate with clinical presentation. See section 2.3.
- Study designs - generalisability.
 1. Studies used human or animal samples derived mainly from the knee, none involved the ankle joint. See section 2.4.
 2. The choice of human joint used for harvest and the location of the sample site may affect results. See section 2.4.1.
 3. It is possible that the type of animal used may have an impact on the generalisability of results. See section 2.4.1.5.
- It has been suggested that because joints of skeletally immature dogs are more susceptible to blood damage in joints, the data may be extrapolated to suggest that young humans are likewise more at risk (Hooiveld, Roosendaal, Vianen, et al., 2003). See section 2.5.1.
- The conclusion that a brief in-vitro exposure to blood (single or limited number) results in lasting damage (Roosendaal, Vianen, et al., 1999) implies that all people with otherwise normal joints should go on to develop a haemophilic-type arthropathy following similar exposure to blood where this is not the case. See section 2.6.

The researcher will now discuss each of these areas.

2.3 Pathogenesis in light of clinical evidence of haemophilic arthropathy

In 2007 Manco–Johnson et al. produced a seminal paper that was the culmination of a longitudinal study tracking the orthopaedic outcomes in two groups of boys on differing treatment regimens. They were followed from initiation of therapy until the age of 6. A total of 18 abnormal joints (13 ankles, 3

elbows, and 2 knees) were detected in 15 children from both intervention arms largely by MRI. Comparison of the total number of haemarthroses with a validated MRI scoring system assessing the degree of joint damage was carried out. This revealed some very intriguing results as some joints had abnormal MRI scores with no recorded haemarthroses, and some had normal MRI scores despite many haemarthroses. Statistical analysis specified this lack of correlation as follows:

- Bone/AC changes with haemarthroses – no correlation, $p = .63$
- Haemarthroses with MRI scores – weak correlation, $r = 0.14$, $p = .02$
- Physical examination (Colorado Haemophilia Pediatric Joint Physical Examination Score) with MRI scores – weak correlation, $r = 0.26$, $p < .001$

The first bullet point raises concerns for the researcher as a basic reading of the statistic would appear to imply that the premise of blood alone inducing joint damage may not be correct. Additionally, the last bulleted point above implies that currently used physical examination methods may not be sensitive enough to detect joint damage in children (adding further impetus to identify clinical tools capable of detecting early HA).

In the absence of a good correlation between joint bleeds and damage, Manco-Johnson et al. (2007) proposed that “chronic microhaemorrhage” into the joint or subchondral bone may be the cause of joint deterioration observed without clinical evidence of frank haemarthroses. This is an echo of a previous proposal in response to ankle arthropathy in the absence of frank bleeding (Soreff & Blombäck, 1980). Neither set of authors elucidated the theory.

The subsynovial layer has been established as the origin of joint bleeds (Stein & Duthie, 1981). Chronic hypertrophied synovium is prone to bleeding due to the

potential of being “nipped” during joint motion and also due to the delicate nature of the new vascularisation. But in healthy tissue, the researcher has been unable to find published evidence of chronic microhaemorrhage of synovial tissue in the absence of frank pathology however it would not be unreasonable to assume a small amount of arteriole rupture and repair as part of normal tissue turn over and there may be situations where this occurs more than would be normally expected for instance during growth.

With reference to the other tissue suggested as a source of microhaemorrhage, subchondral bone, the evidence appears to not support this as the source. In mature and aging subchondral bone microcracks can occur and are a physical manifestation of impact loading (single or chronic) and their purpose is to stimulate local remodelling. The process can lead to increased shear stresses and degeneration. It is clearly stated that these cracks cannot be the conduits for catabolic agents which would have a destructive effect on the AC (Burr & Radin, 2003). In the Manco-Johnson cohort the researcher considers that the young age of participants precludes this scenario.

So, results from Manco-Johnson et al. (2007) indicate a paradox between experimental results and clinical reality with no suggestions for the differences with strong support. This is not unusual in arthropathy research and has also been noted with OA (Andriacchi et al., 2004), this led the researcher to consult literature from OA and other areas for any information that may have some bearing on HA development. Prior to discussing this, it is necessary to understand the impact of the HA research designs.

2.4 Study Designs in Light of Non-Haematological Arthropathy and Articular Cartilage Research

This section will consider the points listed under the “study designs” bullet list

above. The HA pathogenesis literature is limited to biochemistry and the researcher considered of uncertain applicability as previously described. Re-evaluating that literature in light of data generated from other arthropathies and other areas may add clarity to the HA information. It should be noted that the vast majority of OA data considers only the AC.

2.4.1 Choice of site and joint for articular cartilage harvest

If a provision were to be applied to HA research that there were no limitations in terms of results generalisation (e.g. (Roosendaal, Vianen, et al., 1999)), then the implication is that results are relevant to all affected joints. On this basis, it would appear reasonable to hypothesise that there are no inherent differences in the AC of affected joints. However even a brief review of the literature would appear to indicate otherwise.

Various authors have considered differences in AC behaviour at the ankle compared (usually) to the knee. In general, these studies are in association with the development or progression of OA which does demonstrate some similarities to the clinical presentation of HA; many are in-vitro studies. It has been noted that ankle AC would appear to be generally resistant to symptomatic OA and that degeneration does occur but appears not to progress to a symptomatic state (Kuettnner & Cole, 2005). A study of 470 adult talar AC samples, showed 62% with no evidence of macroscopic signs of age-related degeneration often seen in other joints (Aurich et al., 2002). It is therefore a conundrum as to why the ankle has become so preferentially affected in HA.

2.4.1.1 Structural and Biomechanical Variances

Differences in the basic structure of the AC may result in variation in response such as to load or permeability to catabolic factors. Following are structural differences that have been determined in ankle AC compared to knee AC:

- Thinner (Shepherd & Seedhom, 1999) – this may reflect the high joint congruency
- Superficial layer accounts for a greater proportion of its depth (Daniels & Thomas, 2008)
- Chondrocytes in the superficial layer are arranged in planar clusters of 2 – 13 cells and not singly or in pairs as in the knee (Schumacher et al., 2002); suggested to affect distribution of load
- Denser ECM with higher glycosaminoglycan (GAG) content (Treppo et al., 2000)
- Lower hydraulic permeability (Kuettner & Cole, 2005)

The presence of higher dynamic stiffness and lower hydraulic permeability in ankle AC is thought to reflect the altered content of the ECM constituents including collagen. These properties were proposed to protect the ankle AC by allowing it to sustain higher compressive loads without ill effect (Kuettner & Cole, 2005). The denser ECM may also retard movement of molecules through the AC thereby decreasing exposure to external catabolic substances (Treppo, et al., 2000).

Therefore the review of this literature would appear to indicate to the researcher that the ankle AC should be less and not more affected by HA. Perhaps then there are biochemical weaknesses. The next section investigates this potential.

2.4.1.2 Biochemical Variation

The experimental data presented were predicated on markers of AC degeneration, in particular proteoglycan metabolism. It is postulated that catabolic factors play a large role in AC degradation in HA (Fabry, 1989; Roosendaal, et al., 1998). A regional difference in response would be important

to consider as most HA research is conducted on knee samples.

OA has been described as “a disorder of cartilage matrix metabolism with episodes of inflammation superimposed” (Kuettnner & Cole, 2005). During these inflammatory episodes, IL-1 is released from inflamed synovium and it is capable of penetrating cartilage (Kuettnner & Cole, 2005). It has been shown that ankle AC is resistant to IL-1 at catabolic levels (Daniels & Thomas, 2008; Treppo, et al., 2000). This difference in response to IL-1 following experimental chondral injury may be a factor in the variance of progression of OA in the knee and ankle (Kuettnner & Cole, 2005).

The researcher considers that it could be argued that these differences in response to IL-1 and proteoglycan metabolism are due to the environment of each joint and that in-vitro the cells would all respond in kind. In fact this is to a degree true and there were much lesser differences between knee and ankle chondrocytes when stripped of their ECM and allowed to re-synthesise in another environment. However, the response to IL-1 remained unchanged (Kuettnner & Cole, 2005). The researcher considers that this continues to support the supposition that HA in-vitro results cannot be generalised to all joints.

From a series of studies investigating the differences in behaviour of ankle and knee AC, Kuettnner and Cole (2003) concluded that:

- The higher compressive stiffness that is found in the ankle could protect the ankle AC from continuous microtrauma.
- The lack of response of ankle chondrocytes to injurious compression and IL-1 suggested that ankle AC is more resistant to the progression of degeneration.

- The ECM plays a significant role in protecting the AC in the ankle.

These conclusions would appear to refute the researcher's hypothesis at the opening of this section, namely that there are no differences in biochemical and structural make-up in the AC of targeted joints. Rather, differences noted suggest that the ankle should be to a degree protected. Inducing from this, the researcher therefore suggests that the presented evidence even more strongly supports the theory that there must be other factors affecting propensity to develop HA at the ankle.

2.4.1.3 Site in the joint

It would appear that the choice of AC harvest site might be relevant to the outcome of investigations observing ultrastructural changes. It has been shown that AC has differing properties dependent on its location within a joint and the loading to which it has been exposed. Areas within a joint that experience little or sporadic weight bearing show fibrillation by teenage years whereas areas with high load and contact are best preserved (Carter et al., 2004). The location of AC samples in HA literature has been described as taken from the femoral condyles and tibial plateau but the exact location is not described therefore it is not possible to definitively know whether fibrillation noted and associated biochemical changes were the result of blood exposure or harvest site (Roosendaal, Koppele, et al., 1999; Roosendaal, et al., 1998). Recent studies have also used AC harvested from the human shoulder (van Vulpen, 2015) that is unlikely to undergo similar loading to any of the highly affected HA joints, particularly the ankle.

2.4.1.4 Choice of animal models

It is difficult but not impossible to perform experimental research on human subjects. For OA, RA and some Anterior Cruciate Ligament (ACL) research

samples have been taken at the time of surgery but this precludes examining factors that might play a part in early disease progression; hence the need for animal models but which models? Malda et al. (2012) examined the AC cellularity, thickness and ECM composition of 48 species ranging from mice to elephants. An inverse relationship between AC cellularity and body mass was found, which was particularly marked with lower weight animals. This is important because higher cellularity in lighter species may impact positively on ability to regenerate AC. In the HA literature, in vivo study data derives mainly from beagle dogs and mice. It was found that the DNA content (representative of tissue cell density) was near 900 ng/mg for mice, 289 ng/mg for beagles and only 71 ng/mg for humans. The authors state that this underscores the need for the use of appropriate in-vivo models that approximate the human situation. It is suggested that horse AC is the most apposite species for mimicking human research as it was found to have comparable thickness and organisation (GAG, collagen and DNA content with depth) and it is possible to take samples such as synovial fluid from the living animal. A final point made by the authors was species longevity, expressly, that smaller animals do not allow long term follow up (Malda et al.). The researcher also considers that it is difficult to scale up given animal time frames into human years in order to translate into clinically useful data. Therefore in terms of the HA animal research presented, it is necessary to consider the cross-species applicability. The researcher considers that the higher cellular count in beagles may partly account for results in in-vivo experiments (Jansen, et al., 2009; Roosendaal, Koppele, et al., 1999) making the results less easy to interpret.

Before leaving this section, the researcher would like to present one final observation regarding study design, which is the choice of measured variables. Several of the HA studies have focussed on proteoglycan metabolism as the

main measured variable (e.g. (Hooiveld, Roosendaal, Vianen, et al., 2003; Roosendaal, Vianen, et al., 1999)). In contrast, studies of OA and post-ACL reconstruction knees have focussed on type II collagen metabolism. It was found that in the ACL knees type II collagen degradation 1 - 8 years post injury was as extensive as in late stage OA despite no clinical evidence of secondary OA. There was only a non-significant trend for reduced proteoglycan and no change in water content (Price et al., 1999). Another study reviewed proteoglycan levels in-vitro following a compressive AC injury after noting that progressive loss from the ECM is a reported feature of early OA. Despite statistically significant loss of GAG, only 1- 2 % of total content was gone. Authors concluded that in this model the GAG loss may be due to mechanical disruption of the AC and not enzymatic degradation despite levels of cytokines used being “probably much higher” than in-vivo levels (Patwari et al., 2003). Finally Bank et al. (2000) hypothesised that the loss of tensile strength in OA AC was due to impaired collagen function and not due to loss of proteoglycan. Using changes in amount of tissue swelling and instantaneous deformation (markers of tensile strength), Bank et al. (2000) deduced that both of these correlated strongly with each other and collagen degradation; there was no correlation with proteoglycan content. The authors also cited other papers that showed the removal of proteoglycan by various means did not alter tensile stiffness or change the spatial configuration of the AC (Bank et al., 2000).

HA research considering AC health has focussed mainly on proteoglycan metabolism, however the above research considers AC function as a whole and would appear to suggest that collagen metabolism might be a better indicator of the overall health (ability to function) of the tissue. The researcher holds the view that markers of collagen turnover might have generated results more representative of AC health than those generally used in the HA literature.

2.5 Pathogenesis in Light of Articular Cartilage Evidence

It is important to understand the behaviour of AC in order to interpret evidence.

2.5.1 Cartilage maturity

The maturity of AC has been posited as a factor for the development of HA.

Researchers noted that the effects of blood on cartilage in an in-vivo experiment appeared to be greater in younger dogs than mature ones (Hooiveld, Roosendaal, Vianen, et al., 2003). Additionally, certain proposed non-haematological contributory factors are also more marked in childhood such as reduced proprioceptive acuity (discussed in Chapter 3). This is worth further consideration as the clinical implication could be that the effectiveness of an intervention might be age dependent.

A biochemical and histological analysis was carried out following blood exposure of harvested AC and synovial tissue from dogs of different ages determined by radiological skeletal maturity (Hooiveld, Roosendaal, Vianen, et al., 2003). Results showed that the youngest, skeletally immature dogs showed the largest deviations from control samples in many metrics linked to ECM turn over. From these results it was concluded that young dogs, and therefore young humans, were more at risk of sustaining AC damage from joint bleeds (Hooiveld, Roosendaal, Vianen, et al., 2003). This raises two queries for the researcher:

- a) Is the AC in a *skeletally* immature dog (or human), immature?
- b) Is there other evidence that AC maturity is a consideration for vulnerability?

Addressing point a) it would appear that the answer is no. Adult AC across species demonstrates a formation known as the Benninghof Structure (BS)

which consists of three zones as shown in Figure 2.1. At birth these zones do not exist and the AC presents an homogenous character, with the collagen fibres largely parallel to the articular surface. The development of these zones has been mapped and is time dependent. The BS becomes established by the time an animal achieves sexual maturity (van Turnhout et al., 2010) which occurs in advance of skeletal maturity in humans and other species.

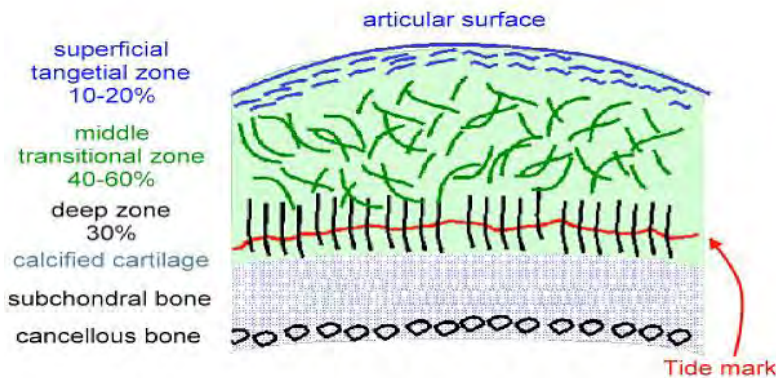


Figure 2-1 Representation of the Benninghof Structure in Articular Cartilage (Source: <http://ernestschilders.com/hip-anatomy.php>)

This would imply that the dog model described above (immature equalled “dogs under 1 year”) may not reflect AC immaturity as sexual maturity in a dog is related to its breed and size. The beagles used reach maturity at around eight months old (Goedken, Kerlin, & Morton, 2008). Notwithstanding this potential limitation in methods, there still may be some validity to the conclusion drawn.

The development of the BS is a functional response to loading. Within a joint different areas of the articular surface are used for different types of weight bearing; either constant low load or intermittent high loads. It has been shown that in order for development to be effective, the young animal must exercise and load appropriately (Brama et al., 2002; Brommer et al., 2005). Appropriate loading has been suggested as the most important preventative factor when attempting to protect from joint injury later in life (Brommer, et al., 2005; Kuettner & Cole, 2005).

This was illustrated in a study of grouped foals that demonstrated differing site specific AC development. Exercise-restricted foals showed reduced collagen content and did not develop further collagen after 5 months of age when allowed to exercise (5 months old in the horse is approximately equal to 11 years in the human (Gray, 2013)). It was suggested that the collagen network is incapable of making changes at this late stage (Brommer, et al., 2005). The researcher considers that this finding is potentially extremely important as withholding exercise in early years could have long term consequences for the functional adaptation of AC; there would possibly be consequences for injury resistance capability. The application of this result to the clinical case in question may mimic restricting activity in a young severe haemophiliac, as the restricted foals were weight bearing but limited to a stall.

Another attribute of AC that alters with development of the BS is hydrostatic pressure. This may be of relevance if AC is exposed to toxic by-products of blood or catabolic agents. Collagen arrangement influences interstitial pressure (van Turnhout, et al., 2010). Motion of fluid through AC has been modelled showing that the direction of collagen fibres affected flow. AC under no pressure is both anisotropic (directionally dependent) and inhomogeneous with respect to permeability (Federico & Herzog, 2008). The researcher considers that this might imply that in undifferentiated immature AC the flow would be almost wholly parallel and that any substance able to enter would have unrestricted motion along the collagen fibres facilitating degradation. With maturation, the BS increases hydrostatic pressure potentially retarding the passage of extra-cartilaginous substances (van Turnhout, et al., 2010) implying that immature AC may not perform the same task.

Therefore the researcher considers that there may be some merit in the

supposition that the maturity of AC can affect its behaviour, altering its ability to withstand load and potentially altering the retardation of catabolic substances.

2.5.2 Loading Effects on Articular Cartilage

It has been stated succinctly that joint development, maintenance and degeneration are regulated by factors introduced by loading and motion (Carter, et al., 2004). From a mechanobiologic perspective, intermittent hydrostatic compressive pressure has been shown to have a chondro-protective effect whereas intermittent shear stress will eventually accelerate AC growth and ossification by promoting ECM degeneration and vascular invasion (Carter, et al., 2004). That is, AC is designed to accept high compressive loads and low shear stress (McKinley et al., 2004). It has been stated that resisting shear stress is a primary property of the collagen network (Lane Smith et al., 2000). Shear has also been shown to increase production of oxidants (Martin et al.), matrix metalloproteinases and interleukins (Andriacchi, et al., 2004) which can be catabolic to the AC. Chronically increased shear will lead to a fracture of the collagen fibrils leading to increased surface fibrillation (Andriacchi, et al., 2004). Shear stress is thought to increase in the presence of joint instability, malalignment or articular surface incongruity (Carter, et al., 2004) and these can occur for a number of reasons such as trauma or hypermobility. The researcher considers that shear may be an important piece of the HA pathogenesis puzzle that cannot be encompassed in a biochemical model.

2.6 Unimodal Blood Exposure Theory in Light of Evidence from Orthopaedic Literature

For a unimodal pathway hypothesis for the pathogenesis of HA to be true, other situations where normal AC is exposed to blood, should produce the same effects. There are several examples of this. One such example is the surgical

technique of microfracture which promotes fibrocartilaginous healing within a joint. Looking at case series' of microfracture for talar osteochondral lesions it can be seen that no overt arthropathy development or any of the early disease markers noted in HA such a chronic persistent synovitis and loss of motion are recorded (e.g. (Becher et al., 2010; Chuckpaiwong, Berkson, & Theodore, 2008)).

ACL injury and reconstruction is another example and has a large body of literature concerning long term prognosis. Following this injury there is immediate and copious bleeding into the joint which can persist for several days (Jairaj, 2011). Whilst the development of OA is a potential long term complication of the injury irrespective of whether the ligament is reconstructed (e.g. (Leys et al., 2012)), the researcher was not able to find any evidence of a clinical HA-type presentation. In this and other cases of orthopaedic trauma, the joint is exposed to blood both as a result of the injury and additionally as part of the surgical repair process. These blood exposure examples appear to not support the minimal blood exposure theory previously described, though what is meant by minimal is never clarified.

HA research has suggested that there is an inflammatory component to the process of HA development (Fabry, 1989; Roosendaal et al., 2008), which may have some support in the ACL literature. Levels of ECM fragments, proteases and cytokines detectable in synovial fluid, blood and urine are increased within days of ACL injury and are sustained at elevated levels over a period of years (Lohmander et al., 2007). In particular levels of leukocytes are raised and sensitised to produce more catabolic substances (Borsiczky et al., 2006). This release is proposed to result in a rapid onset of damage to the collagen network and certain ECM components. This may make AC less resistant to loading until

anabolic mechanisms have been activated and have attempted repair (Lohmander, et al., 2007). Although it should also be noted that the relationships between biomarkers and the loading environment (and hence health) of AC are poorly understood (Andriacchi, et al., 2004). The researcher considers that, on this basis, synovial irritation may be the relevant consequence of blood in the joint.

2.7 Synopsis and Conclusions

With respect to the pathogenesis of HA at the ankle, the researcher believes that the current published biochemically-based evidence may not be comprehensive for the following reasons:

- Conclusions drawn are mainly from experimental in-vitro and in-vivo canine studies using AC samples drawn from the knee joint.
- Structural and biomechanical differences in ankle AC may also preclude generalising knee data to the ankle.
- Experimental data based on knee AC cannot be applied to the ankle due to differing responses to the substances used such as IL-1.
- Beagle and mouse data may not be applicable to humans where the horse has been suggested as a more comparable species in terms of its AC.
- It is unclear where AC has been sampled from in the HA studies which may affect its status and so results.
- A prospective cohort study has produced results at odds with the experimental data.

Furthermore, if AC sustains permanent damage after minimal exposure to blood, then it is the researcher's opinion that this should be detectable in other

condition groups. Rather it would appear that authors investigating these conditions are suggesting that other factors such as BMI, history of trauma and increased antero-posterior ankle joint laxity may be relevant precursors to arthropathy development (Chuckpaiwong, et al., 2008). The researcher considers that the literature reviewed in this Chapter is an indication that the pathogenesis of HA may be more complex than previously suggested and supports the need for wider investigation of HA pathogenesis. Daniels and Thomas (2008) stated that pathogenesis of OA is a combination of anatomical, biomechanical and metabolic factors. This chapter has alluded to the potential of other factors such as shear stresses to affect AC function. The next chapter expands on this to discuss anatomical and biomechanical factors at the ankle that may have an impact on the development of HA.

3.1 Introduction

In the era of prophylaxis the ankle or talocrural joint has highest prevalence of HA, the reasons for which remain unclear. A review of the HA literature does not reveal any explanations for the high incidence of ankle HA beyond the contention that basic hinge-like joints are at risk due to high torsional strains (Buzzard & Heim, 1995). Indeed as discussed fully in Chapter 2, the ankle joint should be somewhat biochemically and metabolically protected by the structure and make-up of its articular cartilage (AC). It is the researcher's contention that the pathogenesis of HA is likely to follow a pathway similar to that proposed for OA. This chapter will therefore follow through with this suggestion by reviewing the pertinent anatomical, biomechanical and pathomechanical aspects of the ankle joint in order to present a cogent alternative pathogenesis hypothesis. For the purposes of this review, the motion of the rearfoot will be considered. This will be referred to as the ankle joint complex (AJC).

This chapter is a narrative review and published literature was searched using Medline and Google Scholar initially in 2012/2013 and repeated in 2016. Owing to the necessity of investigating several subject areas within the chapter, groups of search terms were used and included: (gait* OR walk*), (spatiotemporal OR kinetic* OR kinematic* OR energy*), (paediatr* OR pediatr*), (haemophil* OR hemophil*) etcetera. Information has been sourced from both books and articles, with respect to the latter, studies have been included that are experimental designs, observational studies, epidemiological studies and reviews, and books have also been considered. Searches were limited to the year 2000 onwards and articles were written in English. Having identified key

articles, their reference and citation lists were perused for further information sources.

3.2 Anatomy, Motion and Stability

The AJC is comprised of the talocrural and subtalar joints and the inferior tibio-fibular syndesmosis. The latter articulation was not relevant to this study and so will not be described. The purpose of the AJC is to transmit load and to provide the motions of dorsiflexion (DF) and plantarflexion (PF) to enable walking.

Further it acts as a torque converter transferring internal and external rotatory lower limb forces to the foot and ground, and transferring foot

pronation/supination forces to the leg. The talocrural joint is formed from the tibial plafond (trochlear surface) and malleolus, fibular malleolus and the superior talar dome. When considered in isolation, it is described as a modified hinge joint allowing DF and PF. Most DF/PF occurs in the sagittal plane but there are some small additions from the transverse and frontal planes (Kleipool & Blankevoort, 2010).

The talocrural joint capsule is relatively loose antero-posteriorly, but tight medio-laterally allowing motion that is largely limited by bony configuration rather than by itself and ligaments. Its main supporting ligaments are: anterior talofibular, calcaneofibular and posterior talofibular laterally and the deltoid ligament medially (Kleipool & Blankevoort, 2010). Figure 3.1 shows the AJC from the lateral aspect.

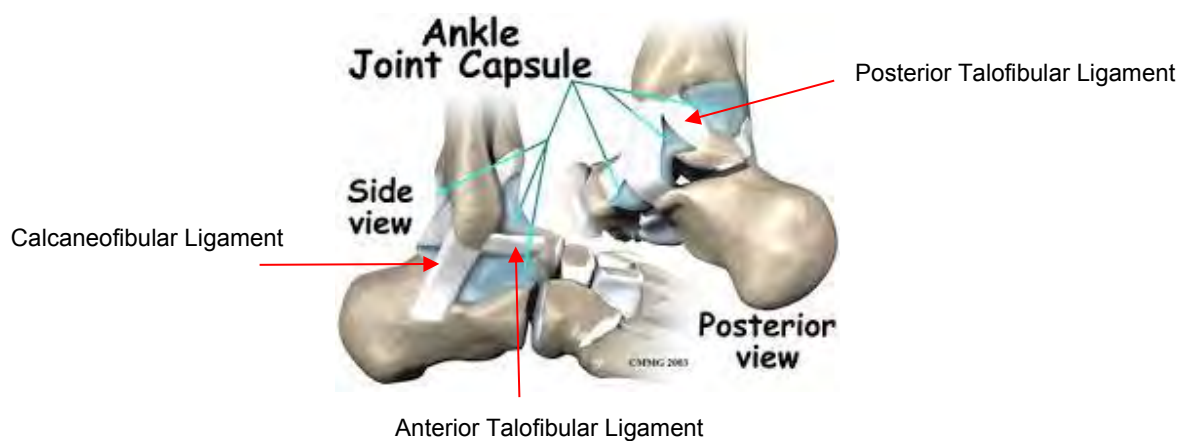


Figure 3-1 Lateral Aspect of the Ankle Joint Complex (source: <http://eorthopod.com/ankle-anatomy/>)

The subtalar joint is formed of two articulations between the talus and the calcaneus: anterior and posterior, with separate capsules. The joints are separated from each other by the sinus tarsi and the tarsal canal. The two joints share a common axis of rotation which lies approximately 42° up from the transverse plane and 23° in from the sagittal plane. A great deal of inter-individual variation exists in this axis and it is suggested that this may influence the motion available (Kirby, 1987). There are several strong deep ligaments supporting this joint. They are extensive and not well understood. The motions available at the subtalar joint in the frontal plane are inversion and eversion (Kleipool & Blankevoort, 2010) however this does not usually occur independently of other rearfoot motions.

It is important that the researcher makes clear their choice of nomenclature. There is some inconsistency in the literature regarding the labelling of motion at the subtalar joint with a lack of clarity of whether pure frontal plane or the complex triplanar motion is being described. Part of this inconsistency is derived from transatlantic preferences. Some sources may refer to the frontal plane motion at the subtalar joint as abduction/adduction whereas recent sources,

particularly electronic are preferring inversion/eversion. The researcher will use the terms inversion and eversion.

The articulations of the AJC work together allowing co-ordinated rearfoot motion. It is considered that DF/PF occur in the sagittal plane, inversion/eversion in the frontal plane and internal/external rotation in the transverse plane. However, in reality the axis of the foot's motion is oblique and aligned with the long axis of the leg. When motion is considered about this axis, what actually takes place within the AJC is best described as pronation and supination, see Figure 3.2.



Figure 3-2 Motion of the rearfoot showing pronation on the left, neutral in the centre and supination on the right. (Source: <https://skimoves.me/tag/supination/>)

Maximal range of motion for DF and PF is 57° , SD 10° where two-thirds is PF. For inversion/eversion range varies from 17° - 23° , SD 4° . During functional activity such as walking and running, the sagittal plane motion required of both joints is much less than the available maximal motion (Kleipool & Blankevoort, 2010).

There is no or little contribution to AJC stability from its ligaments during loading or motion when the ACJ is operating within functional ranges (Kleipool & Blankevoort, 2010). The talocrural joint becomes highly congruent under load

(Kuettner & Cole, 2005) but remains capable of moving freely. The subtalar joint is also highly congruent (Kleipool & Blankevoort, 2010). It is this congruency that is considered the main determinant of the AJC's stability.

3.3 Gait

It could be argued that the most important functional activity of the foot, and so AJC, is gait. It is described broken down into phases and then these phases are described in terms of spatiotemporal parameters, energetics, kinematics and kinetics. The parameters of gait with relevance to this study are described in Tables 3.1 and 3.2 below. Gait is enormously complex, requiring the integration of many systems and a thorough review of gait is beyond the scope of this chapter, so the reader is referred to "Whittle's Gait Analysis" (Levine, Richards, & Whittle, 2013b) for an overview. It is often postulated that differences in some of these measurable variables are indicative of injury or disease initiation or perpetuation. Looking at it holistically there are three essentials to gait:

- Progression – the basic gait engram produces and co-ordinates rhythmic patterns of muscle activation in order to move the body in a specific direction. Also requires the ability to initiate, terminate and guide motion.
- Stability – establishment and maintenance of appropriate posture, and dynamic stabilisation of the moving body.
- Adaptation – of the gait pattern to meet individual goals and demands of the environment (Shumway-Cook & Woolacott, 2001a).

Table 3-1 Spatiotemporal, Kinematic and Energetic Parameters of Gait derived from Shumway & Woolacott (2001) and Levine (2013)

	Spatiotemporal	Kinematics	Energetics
Parameters	Stride length, step length, cadence (steps per minute), time in stance, time in swing, time in single support, time in double support, base of support, speed	Joint motion, angular velocity and acceleration.	Energy consumption (oxygen consumption) per unit time, energy cost (oxygen cost) per unit distance.
Relevant behaviour in normal gait	Mean cadence for young adults is 112.5 steps per minute. Speed 1.46 ms ⁻¹ . Mean step length 76.3cm. Preferred step length related to energy requirements, higher or lower ones need more energy.	Ankle neutral at heel strike, PF to foot flat (8°), then neutral when loaded. DF throughout stance to a maximum of about 12° at heel off. Rapid PF at terminal stance to 20° at pre-swing. DF (0° -10°) at initial swing to clear foot for swing through. At neutral for heel strike. Foot supinated at heel strike, moves into pronation with loading. Supination occurs from mid- to terminal stance. Mean ranges are 9° eversion - 4° inversion.	Energy consumption increases with walking speed. The cost is higher with very slow or fast speeds. It is higher in childhood, reducing into adulthood. Energy use optimised by transfers between potential and kinetic energy, and by minimising displacement of centre of mass. Greatest energy transfer occurs through vertical motion of the trunk.
Factors that can alter parameters	Speed, ethnicity, age, fitness, height, pain, biomechanical anomalies.	Injury, disease, muscular tightness, and hypermobility.	Speed, age, walking surface, footwear. Muscle strategies or abnormal motion requiring higher levels of agonist co-contraction or control.

Table 3-2 Action of Ground Reaction Force (GRF) and muscular activity in Gait adapted from Thomson (2002) and Lipfert et al. 2014)

GRF Direction to Joint Axis		Joint Moment	GRF Action & Effect – Sagittal Plane	Muscular Action
Loading Response Sagittal Plane				
Posterior Posterior Anterior	Ankle Knee Hip	Plantarflexion Flexion Flexion	20-26% stance. Flexes knee and DF ankle. Resisted by extending torques. Knee stops flexing, starts extending. GRF approaches knee, moving ahead of ankle. Ankle extension torque increases, resisting DF.	Eccentric dorsiflexors Eccentric extensors Isometric extensors
Loading Response Frontal Plane				
Lateral Medial Medial	Subtalar Knee Hip	Pronation Varus Adduction		Eccentric intrinsic and supinators Passive tension lateral knee structures +/- tensor fascia lata Activity hip abductors
Midstance Sagittal Plane				
Anterior Anterior Posterior	Ankle Knee Hip	DF Extensor Extensor	51-64% stance. Extending knee torque decreases. GRF near knee and further ahead of ankle. Knee torque becomes zero, yet knee still extends. DF at ankle still decelerated by increasing extension torque.	Eccentric plantarflexors No active muscles. Passive elongation posterior knee structures Eccentric hip flexors
Midstance Frontal Plane				
Lateral Medial Medial	Subtalar Knee Hip	Pronation Varus Adduction		Intrinsic, supinators (lock out midtarsal joint). Passive lateral tension +/- tensor fascia lata Activity in hip abductors
Terminal Stance Sagittal Plane				
Anterior Anterior Posterior	Ankle Knee Hip	DF Extensor Extensor	78% stance. Zero torque and flexing angular velocity: knee joint buckles. Ankle is about to start PF.	PF activity, eccentric to isometric. Passive tension posterior to knee. Active hip abductors
Terminal Stance Frontal Plane				
Medial Medial Medial	Subtalar Knee Hip	Supination Varus Adductor		Intrinsic and supinators augment GRF to supinate subtalar and produce rigid foot. Passive tension lateral knee structures. Active hip abductors
Pre-Swing Sagittal Plane				
Anterior Posterior Posterior	Ankle Knee Hip	DF Extension Extension	82-100% stance. Lead leg touches down. Knee flexion controlled by small extension torque. PF motion and torque at ankle. Maximum ankle jerk, launching phase begins with increasing velocity, flexion at knee and PF at ankle. Toe off, fast knee flexion and ankle PF	Isometric PF activity via Achilles tendon -stored energy for propulsion. Little knee muscle activity. Hip flexor activity – eccentric to isometric to concentric for initial swing
Pre-Swing Frontal Plane				
Near axes all joints	Subtalar Knee Hip	Very small moments		Body need not develop significant muscle activity to respond to moments.

These elements need to be energy efficient and effective at minimising stress on the locomotor apparatus. Figure 3.3 shows typical gait pattern which is broken into two phases: stance (60%) and swing (40%). Each phase is then broken down further. Overall the goals of stance phase are the generation of horizontal forces to move the body forwards in the desired direction, and vertically, support the mass of the body. The goals of swing phase are the advancement of the swing leg and positioning of it in preparation for ground contact (Shumway-Cook & Woolacott, 2001a). Study specific gait detail is discussed in the following sections.

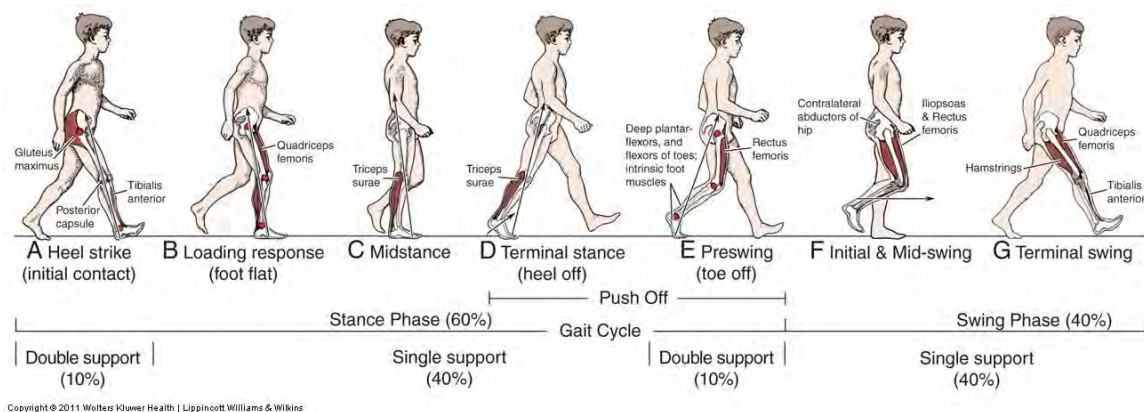


Figure 3-3 Phases of Gait divided into Stance and Swing Phases (Source: <http://epomedicine.com/clinical-medicine/physical-examination-gait/>)

3.3.1 Spatiotemporal

Walking is an activity where one foot is in ground contact at all times. Walking becomes jogging when a speed is reached where both feet leave the ground and there is a float phase. The difference between jogging, running and sprinting is defined by form and parameters such as knee lift and base of support. Walk to run transition occurs over a narrow range of speeds 6.77 – 7.45 kms⁻¹. This may be the point at which peak angular velocity and angular acceleration occur at the ankle. A person's height also has an impact on transition (Shumway-Cook & Woolacott, 2001a). Speed is dependent on

cadence and stride length and so only an alteration in one or both of these will alter speed (Levine, Richards, & Whittle, 2013a). Pathology affecting one leg will result in attempting to reduce stance duration on that side. To do this, the swing leg must be brought to ground more quickly thereby shortening both the swing duration and step length on the “good” side.

3.3.2 Energetics.

Energy efficiency is achieved by the smooth transfer of kinetic and elastic energy (Shumway-Cook & Woolacott, 2001a) and by controlling the excursion of the centre of mass (COM) (Levine, et al., 2013a). There is a child’s swing-like pattern to the movement of energy from potential to kinetic and back again. An example of this is the reciprocal trunk and pelvis rotation which stores potential elastic energy that is released as the trunk de-rotates (Levine, et al., 2013a).

Optimisations to minimise COM excursions and thereby minimise energy expenditure, have been proposed and are known as the six determinants of gait:

1. Pelvic rotation – twisting about a vertical axis brings hip forward as hip flexes and backwards as it extends. Meaning that for a given stride the hip joint moves through a smaller range than the foot and so less hip motion is required.
2. Pelvic obliquity – tipping about an anteroposterior axis raises one side and then the other so that the hip of the swing leg is lower than the stance one. Reduces COM motion as trunk height depends on the averaged hip joint height. (Although it should be noted that studies have shown that the level of the hip can stay level or rise (Whittle & Levine, 1999)).
3. Knee flexion in stance – adjusting the effective length of the leg. Flexion shortens the leg in midstance reducing the apex of the COM excursion.

4. Ankle mechanism – adjusting the effective length of the leg. The contact of the ground by the heel (dorsiflexed talocrural joint) lengthens the leg during the loading response raising the COM.
5. Foot mechanism - adjusting the effective length of the leg. The forefoot effectively lengthens the leg from heel rise as the ankle plantarflexes.
6. Lateral body displacement – side to side motion. Keeping the base of support narrower than the hips reduces the amount of lateral motion required to preserve balance.

(Levine, et al., 2013a)

It has been proposed that only the 5th determinant has any major impact on the COM (Kerrigan, 2003), which may be supported by the finding that muscular demand values for the plantarflexors are highest compared to other lower limb muscles (Requião et al., 2005).

3.3.3 Kinematics

It has been reported that up to 68.1% of available range of eversion is used in stance compared to 13.2% of inversion. An increased susceptibility to injury is postulated in individuals operating towards the extremes of their range in normal walking which would increase in running or under other load putting tissues at risk (Dowdy Youberg et al., 2005). This may be present in individuals with an over-pronated gait pattern or those with limited range.

3.3.4 Kinetics

The branch of gait analysis concerned with kinetics is most often studied when investigating changes in gait parameters and their relation to injury or disease. The researcher considers that the pattern and degree of loading of the AJC may be highly relevant to the initiation of a disease process and so this will be discussed in some detail in subsequent sections.

3.3.4.1 Externally applied forces

One of the main determinants of torque at the ankle is Ground Reaction Force (GRF). This is the force exerted by the ground on the body in contact with it. The GRF vector acts to cause movement moments around the joints of the lower limb. (A moment is the product of force and direction.) How it acts on joints in gait and other tasks like landing has been examined in order to investigate patterns, function and dysfunction. Its action in normal gait is presented in Table 3.3 above. It is often considered broken down into its constituent parts of vertical (v), horizontal (h) and less often, transverse GRF. Briefly, vGRF during walking demonstrates key features one of which is the heel strike transient which is said to occur at about 10% of the gait cycle. It is a passive response to the heel contacting the floor (Verdini et al., 2006). Much research has been devoted to investigating this on the assumption that there must be a link between higher or more rapid peaks, and injury or degeneration in joints. However, results are inconclusive and indeed one author reached the conclusion that impact forces cannot be linked to either acute or chronic injuries based on research up until 2001 (Nigg, 2001). The researcher has seen no conclusive research to challenge this to date. It has therefore been suggested that forces sustained during the heel strike transient are perfectly tolerable by the body under normal circumstances (Nigg, 2001). This response to vGRF would correlate with what is known about articular cartilage behaviour under load. The articular cartilage tolerates compressive load well but does not tolerate shear loading which has been shown to accelerate degeneration (McKinley, et al., 2004). It is also known that articular cartilage develops load tolerance depending on exposure during development leading to areas of the joint surface adapted to constant low load and other areas intermittent high loads (Brommer, et al., 2005). This was discussed in Section 2.4.

Whilst the heel strike transient has been shown to have no effect on injury and degeneration, the actual ankle joint vGRF at heel contact is less than that at propulsion. Eighty-two percent of the peak compressive intra-articular force occurs at the start of propulsion and is thought to be created by muscle action as opposed to the GRF (Procter & Paul, 1982; Scott & Winter, 1990). A recent study corroborates this and states that the high forces at work are the result of release of stored elastic energy in the triceps surae muscles creating the very high peak power and angular ankle acceleration noted by many researchers (Lipfert et al., 2014).

HGRF on the other hand, is only partly responsible for the shear created via internal joint forces; total shear force is created from the muscular and joint reaction forces. HGRF is initially negative or aimed backwards representing a deceleration of the foot but becomes positive as the tibia progresses over the foot. Whereas the internal joint reaction force is negative during the whole of stance phase trying to move the foot posteriorly on the tibia and the muscle reaction force is positive and opposing. The muscles are providing an “anti-shear mechanism” to stabilise the ankle (Scott & Winter, 1990). It has been reported that the joint component of the shear forces is sensitive to the line of action of muscles and a small change in angle of pull of the muscles may have a significant effect on shear (Scott & Winter, 1990). This reading of the literature would imply that insufficiencies of the muscular system may affect the efficiency of the anti-shear mechanism resulting in higher articular cartilage surface shear forces. Furthermore, specific insufficiencies may result in an alteration in direction of applied resultant force which may expose areas of articular cartilage surface not adapted for repetitive load. This proposition is discussed below.

3.3.4.2 Internal forces and articular contact pressures

Impact loading in the leg and foot can be influenced by geometry, ankle and knee stiffness and/or the coupling between the soft/rigid structures in the foot and leg (Nigg, 2001). Alterations in joint contact areas may lead to overload of areas of articular cartilage not adapted to the purpose (Potthast et al., 2008). The talocrural joint articular cartilage is only partially loaded at all times (Wan et al., 2006). It has been concluded that the main loading is anterolateral although there can be variability (Suckel et al., 2010). Due to the high congruency of the talocrural joint, relatively slight changes in position can result in disproportionate changes in articular cartilage contact area (Tochigi et al., 2008).

Lower leg muscles generally have an eccentric action and short lever arms with respect to the talocrural joint and so can be assumed to have a large effect on joint contact pressures. Muscle activity has been shown to affect loading areas, peak and mean joint contact pressure data. Potthast et al. (2008) have shown that the triceps surae muscle group exerts the pull of greatest magnitude, but that smaller muscles have a much greater effect on pressure distribution even with their smaller cross sectional areas when acting synergistically in the mid to late stages of stance. The mechanism for this is not discussed. The authors suggest that the extrinsic ankle muscles excluding the triceps surae appear to act like a tensile bracing mechanism in a co-contraction fashion. The study concluded that ligamentous rupture and muscular insufficiency can alter internal load distribution profoundly (Potthast, et al., 2008). In particular the role of flexor hallucis longus (FHL) has been highlighted, with authors asserting that it can be assumed that incapacitating this muscle for whatever reason would lead to impairment to talocrural joint and foot integrity; this being particularly the case where ligamentous insufficiency was also present. Tibialis posterior muscle had the greatest effect on articular cartilage contact pressure (Potthast, et al., 2008).

FHL and tibialis posterior may both be functionally incapacitated in an over-pronated foot as both muscles are held in an elongated position making recruitment more difficult.

Alterations to loading have been posited to be partly responsible for both degenerative and post-traumatic arthritis (McKinley, et al., 2004; Tochigi, et al., 2008). Cadaveric investigations utilising artificially created aberrations in articular cartilage or instabilities (anterior talofibular ligament dissection) have shown increased loading in adjacent areas and increased mean and peak pressures (McKinley, et al., 2004; Tochigi, et al., 2008). The elevated rates of contact have been shown to be linearly related to the degree of instability.

These instabilities may not be detectable kinematically and may occur in joints with residual minor malalignments or residual incongruity post-insult. These micro-instability events could lead to accumulating damage over years due to localised regions of increased contact pressure in regions of the joint not usually used for weight bearing (Tochigi, et al., 2008). These pre-clinical effects may be taking place in HA when blood is present in the joint causing a temporary instability via muscular inhibition (leading to a lack of joint bracing) or change in intra-articular pressure to a positive value due to blood volume (Wood, Ferrell, & Baxendale, 1988), due to the incident that incited the bleed or due to the articular cartilage changes such as cysts.

Forces acting about the talocrural joint are greatest in early propulsion. It could be inferred that this is when the requirement for control would be greatest.

Given the necessity to control injurious shear on the articular cartilage, ensuring that the triceps surae can decelerate the tibia on the talus and the smaller muscles, particularly FHL and tibialis posterior, can produce an adequate synergy in late stance would seem important to the researcher. With respect to

the much investigated heel strike transient, Nigg (2001) proposes that impact forces are not important for their potential for injury but rather for their effects on muscle fatigue (and thereby less co-contraction in propulsion), work done, comfort and performance.

3.4 Stability and Control of Gait

Coordination of control occurs via highly complex feedback and feedforward neural processes using interplay between perception, cognition and motor systems. A stable dynamic stability system (person or joint) is one where the desired movement is not significantly altered from a given trajectory even when perturbations are applied. Chosen sensory strategies used in gait vary with age, task and environment (Shumway-Cook & Woolacott, 2001b) and factors that put stability to the test include age, walking surface, certain gait parameters particularly speed (Samson et al., 2011) and injury or disease.

At the level of the talocrural joint, during walking, the main four ligaments are slack or minimally tensioned. Ligaments have low stiffness for small strains, small moment arms and their ability to guide and limit joint motion during normal functional activities has been questioned. Stability of the AJC during functional movement is determined by joint congruency and muscle action (Kleipool & Blankevoort, 2010), whereas the ligaments may have more of a sensory function. The muscle action that controls joint motion has been described in Table 3.2.

The hip and knee joints are mainly held in stabilisation configurations during stance phase whereas the ankle joint is driven to propel the body (Dumas & Cheze, 2008). Muscle activity in stance is used for shock absorption and upper body support against gravity (Shumway-Cook & Woolacott, 2001a). Whilst there

is a degree of redundancy in the muscular system, disruption to the preferred recruitment pattern may impact on joint loading thereby exposing joints to risk. In HA where the “damage” is thought to be sustained at a young age there is the possibility that natural development might also expose the AJC to uncontrolled loading. Paediatric gait differs from adult gait and must be considered further.

3.5 Paediatric Gait

Maturation of gait from first walking to mature adult gait has been investigated to ascertain at what point various parameters assume an adult configuration.

Five characteristics of matured gait have been defined:

1. Duration of single leg stance
2. Velocity
3. Cadence
4. Step length
5. Ratio of pelvic span to step width

There is an initial maturation which consists of learning balance control for three to six months after the onset of walking, followed by a second phase lasting around five years in which the locomotor pattern is refined (Shumway-Cook & Woolacott, 2001b). With respect to joint angles, moments and powers there is variation in the literature. Ankle joint mechanics have been reported as mature between 5 and 13 years. Foot mechanics of young children, including GRF, metatarsophalangeal joint and ankle kinematics, and dynamics to define mature foot function, have been explored. Samson et al. (2009, 2011) reviewed 84 feet of 42 participants divided into three mean age groups: 2, 3.5 and 5 years. A group of adults were used for comparison. The main findings were as follows:

- GRF – between group differences were noted at pre-swing in maximum vGRF, hGRF and in mediolateral force in early stance where values are lower in children than in adults. Mediolateral forces are decreased until age 8 and may reflect lack of maturity of more proximal control at the hip. The vGRF and hGRF differences in this peak force appeared to disappear by the age of five (Samson, et al., 2011).
- Ankle – maximum eversion moment decreased with age favouring stability in toddlers. The absorbed energy was maximum at early stance in children and midstance in adults. This could be explained by “roll-off” immaturity associated with lack of medial longitudinal arch or by immaturity of the PF muscles. Whereas the PF moments were similar between groups. Mature talocrural joint moment is acquired between 6 – 9 years (Samson, et al., 2011).
- Duration of the configurations (stabilisation, propulsion and braking) during stance showed that the children seem to mainly stabilise the ankle and propel the hip, whereas the adults mainly brake and propel the ankle and stabilise the hip (Samson et al., 2009).

It has been concluded that except for the talocrural joint, adult like gait parameters occur by age 5. The talocrural joint demonstrates diminished power absorption rates between 3 and 8 years, whilst after 9 years, it was similar to adult rates. Peak power generation was also comparable to adult values at this age (Samson, et al., 2009). Step width (ratio of pelvic span to step width) is similar to adults by the age of 7 (Shumway-Cook & Woolacott, 2001b).

The evidence demonstrates that the talocrural joint lags behind the other joints in terms of achieving adult-like maturity of function. The researcher can conceive that this may indicate a time period when the AJC joints may be

subject to greater shear loading due to less efficient muscular synergy or lower strength levels. By the age of seven most muscle and movement patterning look similar to adults. The importance of the efficiency of the muscular systems in controlling the forces applied to the joints has been emphasised in adults. In adults work done in the vertical control of the body's centre of mass is positive (able to act against gravity) indicating the muscular capability present whereas in children it is negative indicating the opposite. This gradually reverses until the age of four is reached (Shumway-Cook & Woolacott, 2001b). Furthermore children do not achieve adult-like sensory integration until after the age of 12 years. Neither do they use visual information for balance, spatial awareness, etcetera, as well as adults (Peterson, Christou, & Rosengren, 2006). In HA it is feasible that children under seven who are experiencing bleeding into their AJC might be restricted in their activities by pain or externally applied limitations in an attempt to protect the joint. Both of these scenarios may ultimately lead to a counter-productive situation where development of muscular control is retarded. The majority of pure gait analysis in haemophilia has taken place with children however the researcher considers that the development stage aspect of it has not always been taken into account. A discussion of this literature now follows.

3.6 Gait in Haemophilia

Studies exploring gait in PWH are generally exploratory between group comparisons and mostly use paediatric cohorts. The numbers are unavoidably small due to the prevalence of the condition and studies vary in methodology precluding pooling of data. Published results are at times contradictory.

A single study that investigated spatiotemporal parameters in a group of 26 boys (7-17years), where 6 boys had known various joint arthropathy, using

GAITrite® gait analysis, noted differences in all measured parameters in the symptomatic boys (Bladen et al., 2007). The asymptomatic group of 20 boys showed increased time in swing and single support, whereas stance time and double support decreased, the authors proposed that these were sub-clinical changes (Bladen, et al., 2007). Overall results of this study would appear to indicate to the researcher that the symptomatic boys moved more slowly than the asymptomatic boys. Other studies have found no spatiotemporal differences between groups (Stephensen, Drechsler, et al., 2009) or reported different findings where stride and single leg support time were found to be increased (Cayir et al., 2014).

With regards to kinematic and kinetic studies two research teams have undertaken studies in children (Stephensen et al. and Cayir et al.) and one with adults (Lobet et al.). “Paediatric” studies compared boys, aged 7 to 20 years of age with matched controls. Inclusion criteria varied but included a history of bleeding into the ankle or “joint involvement”. No GRF differences have been noted. In sagittal plane kinematics a persistent increased knee flexion was noted throughout the cycle (Stephensen, Drechsler, et al., 2009). A significantly greater DF angle in stance has also been reported (Stephensen, Drechsler, & Scott, 2014) along with reduced hip, knee and ankle sagittal plane motion (Cayir, et al., 2014). Results were not consistent across all studies which may be due to variations in the inclusion criteria.

In terms of kinetics, the knee flexor moment showed greater peaks at several points in stance (Stephensen, Drechsler, et al., 2009). A reduced knee extensor moment has also been noted (Cayir, et al., 2014). The hip extension moment occurred more rapidly and to a greater extent during early support phase and

finally the ankle PF moment early in initial double stance was greater (Stephensen, Drechsler, et al., 2009).

The research team of Stephensen et al. postulated that their observed gait changes in boys with haemophilia might be explained by alterations in muscle architecture such as pennation angle and dimensions, and thereby strength. Reduced isokinetic concentric strength was found in vastus lateralis and lateral gastrocnemius along with reduced cross-sectional areas and muscle thickness. Several morphology factors showed a linear relationship with the gait alterations (Stephensen, et al., 2014; Stephensen, Dreschler, & Scott, 2012). Relationships were stronger for muscle width and thickness than cross-sectional area where the order of difference given is between 1 – 2 mm respectively (Stephensen, et al., 2014). The researcher considers that the clinical relevance of such small dimensional differences may be difficult to establish despite statistical significance and could be explained by other factors such as hydration state. Additionally, the reduced dimensions may not be affecting motor unit recruitment. The authors suggest that this lack of isokinetic concentric strength in lateral gastrocnemius presents clinically as an inability to control forward motion of the tibia over the talus and hence the increased DF motion noted (Stephensen, et al., 2014). It is unclear how an isokinetic concentric measure can be translated into the gait pattern however, if this is indeed the case then this is important as at the point of peak DF occurs just after heel rise, and so forward excursion of the tibia should have ceased (Levine, et al., 2013a). The studies from Stephensen et al. (2012, 2014) cannot define whether the presence of the PF weakness was present before the bleeding into the AJC occurred in their cohort.

A study of adult PWH with multiple joint impairment found that there was an overall increase in the vertical displacement of the COM which was not reflected by a change in the energy cost of walking (Lobet et al., 2013). PWH may have a very efficient recovery of energy using this pattern that may enable them to maintain muscle mechanical work at a reasonable level (Lobet, et al., 2013). This would correlate with the proposal that normal gait can consist of differing strategies to achieve the same goal (Levine, et al., 2013a).

A higher metabolic cost was also determined in PWH which was highly correlated with joint damage. In isolated ankle HA the metabolic cost was proportional to the degree of dysfunction. Less ankle power meant more metabolic energy consumed and reduced walking efficiency (Lobet, et al., 2013). The authors were unable to offer a definitive explanation for the increased metabolic cost in PWH but suggest increased co-contraction of muscles (Lobet, et al., 2013) or as the researcher interprets it, the muscles assuming a greater stability pattern. Another finding of interest is the linear relationship established between age at first joint bleed and walking velocity (Cayir, et al., 2014). It may be recalled that energy cost is related to gait velocity and moving more slowly requires greater energy consumption.

Overall clinical interpretation of the paediatric HA research is difficult. The researcher proposes that interpretation of findings en masse could be that the children are not achieving adult markers of normal gait at the same time as their healthy peers on the basis of their slower walking speed, maintaining a stabilisation muscle activity pattern at the ankle and reduced calf muscle function. It is a possibility that certain determinants of gait maturity could have been delayed in the presence of a number of bleeds by early childhood.

The limitations of the literature reported here are considered by the researcher to be the focus on individual gait parameters precluding the consideration of the whole picture. As discussed above, gait must be considered in terms of the complex interaction of systems and their effectiveness and efficiency in producing walking. The researcher deems that each investigation in and of itself is not explanatory of its own findings. Moreover, some literature exploring the pathomechanical effects of HA has attempted to assign findings aetiological status which the design of the studies precludes. Aetiological determinants that may aid in identifying inciting events or situations for HA could be related to those for the most common cause of trauma to the AJC which has been examined from a mechanistic view point in the next section.

3.7 Pathomechanics at the Ankle Joint Complex

The literature, at least that concerning those living in westernised countries, would appear to indicate that PWH live near to normal lives, only having to avoid activities highly likely to cause bleeding such as contact sports (Beeton, Neal, & Lee, 2005; Schoenmakers et al., 2006). Although, given the popularity of football in particular and the wish to do the same things as peers, the researcher considers it debatable as to how well boys adhere to not kicking a football around in the school playground or park even if they are barred from doing so in physical education sessions. It would therefore not be unreasonable to suppose that the rate of lateral ankle sprains in PWH is similar to that in the general population. Therefore the pathomechanics and consequences of this injury in particular could potentially be enlightening when considering the development of HA. Moreover a link between the occurrences of ankle haemarthroses with traumatic ankle injuries and in particular lateral ankle

sprains has been suggested (Buzzard & Heim, 1995) and recurrent lateral ankle sprains has been proposed to be the primary cause of post-traumatic OA in the general population (Valderrabano et al., 2006).

Over 55,000 lateral ankle sprains are reported per day in the UK (O'Loughlin et al., 2009) and probably just as many are unreported due to the individual's perception that lesser severity levels do not require medical intervention. Meta analysis indicates that overall males sustain 6.94 sprains per 1,000 activity exposures. Children (both sexes) sustain more sprains than adolescents, who sustain more than adults (2.85 vs 1.94 vs 0.72 per 1,000 exposures). Lateral ankle sprains are often considered innocuous injuries however up to 80% of people sustaining one lateral ankle sprain will go on to injure the same joint again (Gribble et al., 2004; Nakagawa & Hoffman, 2004). Residual post-injury complaints have been recorded from 6% to 78% at eight months to three years follow up depending on level of activity and populations investigated (Kemler et al., 2011). More specifically, 30% show evidence of objective mechanical instability and subjective feelings of instability at one year follow up (Hubbard et al., 2007).

The sport category with the highest incidence of ankle injury varies depending on measurement unit. It has been reported as indoor/court sports with a cumulative incidence rate of 7 per 1,000 exposures (the authors produced a unified measure for this systematic review where possible) or 1.37 per 1,000 athlete exposures and 4.9 per 1,000 hours (Doherty et al., 2014). Although another source using incidence per 1000 person-hours rated hurling as the highest general incidence (32.88). Trailed by rugby (8.14), soccer (6.52), basketball (5.20) and triathlon (4.70) (Fong et al., 2009). It should be evident that not all sprains are sport related however the majority of research is in

sporting or active populations and may be relevant to the age population who are largely affected by HA at the ankle.

3.7.1.1 Mechanisms, Clinical Corollaries and Risk Factors

The mechanisms of lateral ankle sprains can be divided into contact and non-contact types. In the former the person makes contact with an object or another player in sport causing the ankle to move into an extreme weight-bearing PF/inversion position (Hertel, 2002). The internal rotation of the talus and inversion of the subtalar joint on the externally rotated tibia subjects the anterior talofibular ligament to severe strain causing damage to its fibres. With increasing load and strain the other lateral ligaments can also become injured. The evertor muscles work eccentrically trying to limit the high velocity supination moment (Lentell, Katzman, & Walters, 1990) and can themselves become damaged. Concurrent damage to the joint capsule and ligamentous stabilisers of the subtalar joint are common. Finally, damage to local nerves has been reported in grade II or III sprains (Beckman & Buchanan, 1995).

The mechanisms for non-contact sprain remain under investigation. Fuller (1999) describes lateral ankle sprains as a dynamic process of subtalar supination. Many authors have attempted to pin down the aetiology of the injury. It has been suggested that the inability to accurately position the foot prior to touchdown may be important. Computer simulated muscle models have demonstrated that a more plantarflexed foot at touchdown leads to excessive supination (Wright et al., 2000). However a prospective study of 222 students did not support this finding (Willems et al., 2005). It did however note a number of biomechanical factors in a group of normal participants who prospectively sustained LAS as follows: "(1) a longer total foot contact time, (2) a higher loading underneath the medial and less loading underneath the lateral border of

the foot, (3) a medially directed pressure distribution at first metatarsal contact, forefoot flat and heel off and less pressure displacements in the intervening phases, (4) a delayed knee flexion, (5) a more laterally directed pressure displacement in the forefoot push off phase and a laterally situated COP (centre of pressure) at last foot contact, and finally (6) a greater extension range of motion at the MTPJ (metatarsophalangeal joint) 1". The authors suggest that these findings may represent the presence of hypermobility in the foot (Willems, et al., 2005). Overall however, lateral ankle sprains most often occur with excessive supination of the rearfoot on an externally rotated lower leg when touching down in gait or landing from a jump (Hertel, 2002) The altered knee flexion findings are interesting and are similar to those noted in haemophiliac children described above.

Extrinsic risk factors cited include side cutting motions and landing on uneven ground as they result in a large supination torque (Wright, et al., 2000). It has also been noted that injury is more likely to occur in competition situations as opposed to training (e.g. (Junge & Dvorak, 2013)) and towards the end or exercise sessions as a likely result of fatigue (Ekstrand, Waldén, & Hägglund, 2004).

A spectrum of residual symptoms has been reported following failure to recover completely from an initial sprain. These have been labelled chronic ankle instability (CAI), functional ankle instability, recurrent sprain and mechanical instability. However, authors' descriptions of the various distinct labels are overlapping and maybe a reason for some inconsistent investigative results seen. Whilst work has been done to attempt to clarify this situation (Hiller, Kilbreath, & Refshauge, 2011) much of the published work has used these labels and so the researcher will do likewise within this chapter.

Intriguingly and somewhat akin to HA, only a small percentage of people sustaining initial lateral ankle sprain go on to develop residual symptoms. People that do not develop ensuing symptoms have been dubbed “Copers” and have been used to try to identify differences between themselves and those who do develop symptoms. A theme has emerged from these studies where forefoot differences are thought key and potentially rearfoot or impact factors less important. An increase in eversion in mid to late stance and in jumping tasks has been reported (De Ridder et al., 2013; Wikstrom et al., 2012) and linked to peroneus longus efficiency and in particular its ability to control the first ray in stance (De Ridder, et al., 2013). De Ridder et al. (2013) found no remarkable differences between CAI participants and copers with respect to kinematic variables in walking and running and suggested proprioceptive, strength and coordination differences. A study taking an alternative tack by comparing the efficacy of outcome measures at identifying CAI versus copers found that self-reported disability indices were more accurate than sensorimotor outcome measures. Authors concluded that due to the variety of outcome measures capable of identifying CAI, that the cause was probably multifactorial (Wikstrom, et al., 2012), tying in with the researcher’s premise regarding HA, where the those who do not develop HA despite sustaining ankle joint bleeds could be considered analogous to lateral ankle sprain copers.

If the spectrum of disorders are considered en masse, various factors have been identified that may influence presentation. Authors have attempted to correlate predictors of lateral ankle sprain or chronic ankle problems in prospective, retrospective and in laboratory-based studies. Research output is sometimes contradictory, even the systematic reviews, perhaps reflecting the differing inclusion/exclusion criteria, measurement techniques and study designs. A potential caveat regarding retrospective studies is the difficulty

determining if any factors proposed to influence the occurrence of lateral ankle sprain were mechanistic.

Several factors appear to be well supported according to systematic review.

These are: increased postural sway (de Noronha et al., 2006; Hiller et al., 2011; McKeon & Hertel, 2008); postural control (Hiller, Nightingale, et al., 2011; McKeon & Hertel, 2008; Riemann, 2002); altered peroneus longus function (Hoch & McKeon, 2014); foot posture in gait (Hiller, Nightingale, et al., 2011); decreased DF range (de Noronha, et al., 2006); general joint laxity (Dallinga, Benjaminse, & Lemmink, 2012); decreased concentric inversion strength (Hiller, Nightingale, et al., 2011); and altered talus architecture (Hiller, Nightingale, et al., 2011).

However, these systematic reviews are not inclusive of all contenders for influential factors or they have concluded that current research output is showing mixed results. The researcher considers that other factors are supported by at least one well designed study in the current literature and so are worth consideration as potential factors in investigating HA. These other potential factors accordingly are: history of previous sprain (Nakagawa & Hoffman, 2004; Tyler et al., 2006); Body Mass Index (BMI) (Beynnon, Murphy, & Alosa, 2002; Dallinga, et al., 2012; Tyler, et al., 2006); proprioception (Hiller, Nightingale, et al., 2011; Nakagawa & Hoffman, 2004); and biomechanics (De Ridder, et al., 2013; Terada et al., 2013; Willems, et al., 2005). Strength related factors are less well supported but clinical evidence supports their consideration. The evidence pertaining to the function of the evertor and PF muscles in gait and landing has been established and so pre-existing deficits in these in terms of strength or timing might be expected to impact injury risk.

Interestingly, specific lateral ligament laxity has not been found to be a risk factor. Fuller (1999) has argued that as the supination moment occurs in advance of reaching ligament tension and that any observed laxity could be an effect rather than a cause or recurrent sprains (Fuller, 1999).

Most researchers have chosen to investigate specific factors or related groups of factors such as kinetic factors. Many of the factors listed above could be said to contribute to the production of efficient and effective motion. This leads on to the supposition that alterations in them would result in a reduced ability to control motion most of which is performed at a subconscious level. What these studies do not explain is why these dysfunctions are present. Moreover, only differences determined prospectively can be deemed risk factors for initial sprain with some certitude. Nonetheless, differences are present and some may be responsible for the perpetuation of symptoms. Rationales for changes detected have been suggested including alterations to feedforward and feedback programming although the literature discussion behind this is again mixed (Bullock-Saxton, Janda, & Bullock, 1994; Caulfield et al., 2004; Hertel, 2008). Other physically obvious reasons are known such as reduced DF secondary to triceps surae tightness during growth spurts (Tabrizi et al., 2000).

To the researcher and the numerous investigators whose work is mentioned above, these factors represent the possibility to intervene and alter the potential for people to sustain sprains. If, as the researcher proposes, there are a similar factors pertaining to the initiation and/or perpetuation of HA, the potential to make changes to prevent or slow the condition may be comparable.

3.8 Presenting a New Paradigm

This chapter has presented an overview of gait and its analysis, and the key role of the AJC complex within it. Evidence has been presented showing the large torques and forces that it sustains and generates. It has shown that the phase of interest in gait may be late stance rather than heel strike. The factors with the potential to influence this, triceps surae, flexor hallucis longus and evetor muscle strength and co-ordination, reduced DF range, hypermobility within the foot and applied external forces etcetera, have been discussed. The recurring theme that appears to emerge is that the complex action of walking requires control of and from multiple systems and that preventing injury may have to reflect this.

Clinicians within the HA arena, at least partially, concur with the researcher as interventional studies have been undertaken in cohorts with HA at the ankle looking at the effects of controlling the ankle and foot in gait by various means (Buzzard & Heim, 1995; Filho, Battistella, & Lourenco, 2006; Lobet et al., 2012; McLaughlin, et al., 2010; Querol et al., 2002; Seuser et al., 1997). The researcher interprets this as a belief amongst investigators that improving gait efficiency will improve the clinical outcomes.

Undertaking the review of literature on haemophilia, HA, other arthropathies, articular cartilage and the AJC has made the researcher aware of the tremendous complexity of the arena and led to the conclusion that research approaches not acknowledging this may end in unconvincing results. Therefore the researcher considered the determination of whether potential factors could affect the development or perpetuation of HA to be a rational way forward in establishing a baseline for future interventions. Building on the information gathered in Chapter 2 regarding HA development and parallels with other

arthropathies, the researcher presents an alternative paradigm for HA development based on a framework for OA development by Andriacchi et al. (2004) and the information gathered on which the current research programme is built. This is presented in Figure 3.3 and adds an inciting event level to the framework acknowledging the possibility that this could be singular or multiple events. It also acknowledges the potential for things external to the physical person to influence HA development. It then marries this information with an articular cartilage model with loading and shear and considers their effects on articular cartilage metabolism and their capacity for causing damage.

3.9 Conclusion & Research Questions

The literature review covered in Chapters 2 and 3 together with clinical observation has therefore led to the researcher to develop the following overarching research question:

In what ways do non-haematological factors contribute to ankle arthropathy in people with haemophilia and how can these factors be identified?

Several subsidiary questions are also suggested:

- 1. What level of agreement can be achieved amongst an international panel of haemophilia clinicians regarding the identification and importance of factors with the potential to influence the development of haemophilic arthropathy?*
- 2. Are selected clinical instruments suitable for use with PWH?*

3. *What instruments with high clinical utility are able to discriminate between those PWH with and without early ankle haemophilic arthropathy?*
4. *To what degree if any, are investigated factors related to the presence of haemophilic arthropathy?*

Addressing these research questions required an expansive and integrated approach. The following chapter describes the methodological and research design approaches chosen by the researcher in order to address this intricacy.

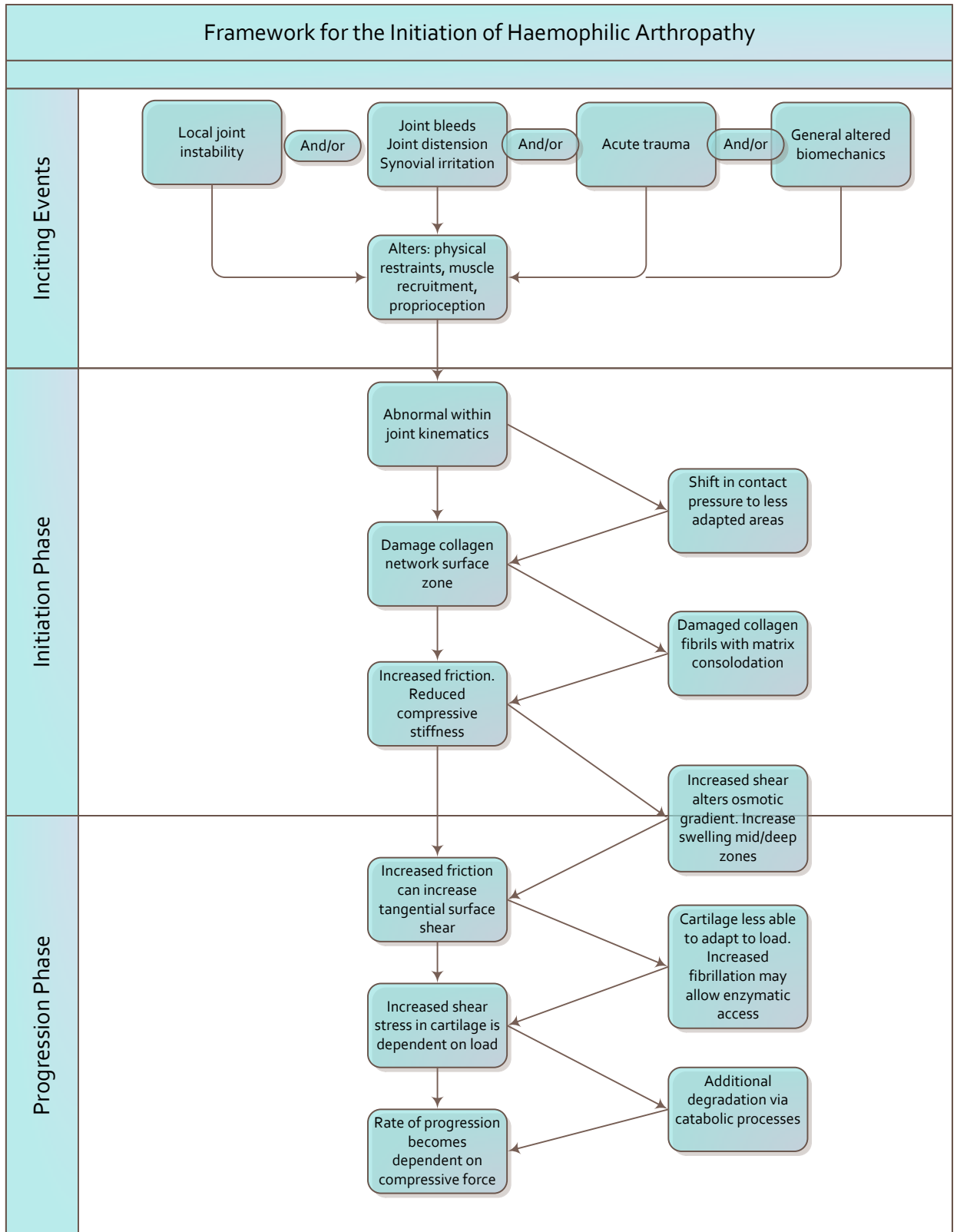


Figure 3.3, Proposed Framework for the Development of Haemophilic Arthropathy adapted with permission from Andriacchi et al 2004.

4.1 Researcher's Perception of the Study

The researcher's motives for undertaking this research were presented in Chapter 1, however her expectations and assumptions with respect to the research question were not discussed. In undertaking this study the researcher was seeking to gain an understanding of factors that have the potential to influence the development of haemophilic arthropathy (HA). In doing so it was hoped that a tool would be developed which has the power to improve the lives of people with haemophilia. The focus was on the clinical utility of the tool. The researcher was not seeking to gain an understanding of the HA itself, per se, or the lived experiences of those with the condition, but instead was seeking practical or "Real World" solutions to a clinical problem, that is the development of HA. In undertaking this, the researcher acknowledged that she had preconceived ideas of what factors might influence arthropathy development, how they might operate and how to address them. Furthermore, she considered that investigation into this area was likely to produce a complex picture. The awareness of these preconceptions made the researcher approach the study in such a way as to ensure that her biases could not adversely affect the research results and led her to an approach encapsulated by the "Real World Research" (RWR) concept as described by Robson (2011).

A real world researcher is described as:

- Interested in solving problems
- Interested in getting large effects (robust results) and concerned about achieving actionable results
- Generally working in the "field" as opposed to laboratory based research

- Operating under strict time and cost constraints
- Needing to be generalist researchers (familiar with a range of methods and approaches)
- Orientated to stakeholder

(Robson, 2011c, p.11)

The researcher had theorised that the development of HA is multifactorial however this has not been reflected in the literature. The available research base, at least with regards to musculoskeletal issues in haemophilia, is very much laboratory based (e.g. Stephensen 2009); whilst it contributes to the knowledge base it is unimodal and has no direct application to clinical care and so is not immediately enhancing outcomes for patients. These studies do not directly follow a mechanistic approach and there are no links to how or why; they are on the whole reductive in design. The implication of this is that available literature is not enlightening with regards to finding actionable results to help ameliorate the impact of HA; there is no real world applicability. An alternative methodology was indicated and this needed to be driven by the research question suggested by the problem at hand: In what ways do non-haematological factors contribute to ankle arthropathy in people with haemophilia and how can these factors be identified?

For this question the researcher considered an exploratory approach necessary. In order to try to limit any unintentional researcher bias, a first subsidiary-question relating to the identification of factors with the potential to influence arthropathy development was formulated. This then needed to be followed by how to assess the influence of any identified factors. However whilst the researcher tried to limit bias, Foucault acknowledged that it was impossible to write and not impart something of oneself. The very act of interpretation involved the writer in a close interaction with that being analysed and discussed

and so, to a degree, the writer does reveal something of themselves (Oliver, 2010a, p.84). So, in order to structure this research project, the researcher sought a framework within which to operate and which would help fully realise the research subsidiary questions and data gathering directions.

4.2 Conceptual Framework Underpinning Research Methodology

Foucault advocated research methods that allowed all lines of enquiry to be kept open in order that possible solutions to problems did not become obscured. This practical approach might be considered to be in keeping with the true nature of scientific enquiry (Oliver, 2010c, p.140). The researcher also felt that it might be necessary to use multiple approaches, potentially concurrently, to effectively address the main research question. This led the researcher to use a conceptual framework based on Meeuwisse et al.: A Dynamic Model of Etiology in Sport Injury: The Recursive Nature of Risk and Causation (Meeuwisse et al., 2007). The proposed model recognised that the risk of injury is dynamic and a person's susceptibility to injury may alter on a daily basis depending on various factors; there is no linearity to the process. This implies that the truth of causality varies on any given day. The authors suggest that this may be why there has been such variability in causality study results and why we are not much further along in determining potential aetiological factors for various injuries (Meeuwisse, et al., 2007). This is illustrated for haemophilic arthropathy in Figure 4.1.

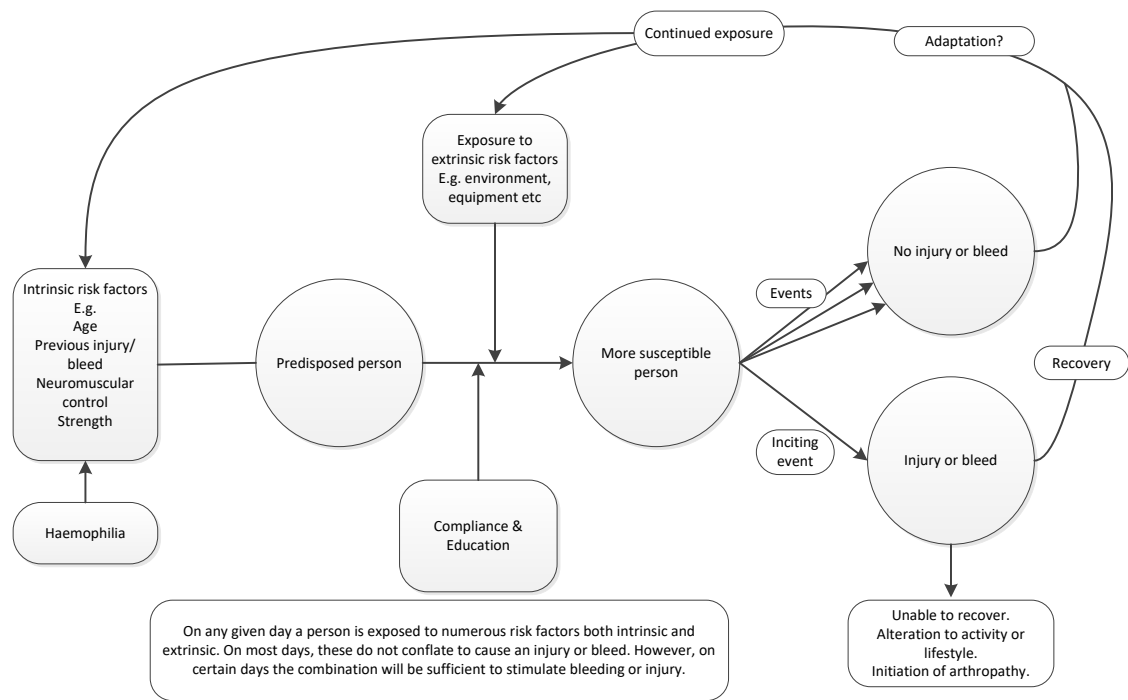


Figure 4-1 A dynamic, recursive model of injury adapted with permission from Meeuwisse et al. 2007.

Based on this, my working theory was that the action of bleeding into a joint is a situation where the outcome is HA only in certain contexts. It could be that the presence of a combination of independent variables such as hypermobility (intrinsic) or poor exercise choices (extrinsic) may be the context required for HA to develop. The researcher judged it unlikely that the presence of a single one of the proposed factors would be explanatory but rather a group interacting according to the environment on any given day may lead to a joint bleed and thereafter arthropathy. This could mean that there are certain factors that can be positively influenced in order to reduce the relative risk on any given day. The contexts within which these mechanisms operate need to be describable (Robson, 2011b, 33). This conceptual framework, required supporting with an apposite methodological approach.

4.3 Methodological Approach

In choosing a methodology the researcher must answer the question: what is the best way to investigate my research problem? Broadly speaking the structuring of the overarching research question required the researcher to identify factors (or mechanisms) that influence an outcome (development of HA at the ankle) as these remain unknown. The working theory described above, was developed based on literature review and clinical experience, but required support and validation from the experts in the haemophilia community. Therefore a broad exploratory approach was needed. This might signify an emergent theory approach which is traditionally associated with qualitative research methods. However, the aim of the study was to arrive at outcomes with clinical utility and using a purely qualitative data collection approach may not achieve this aim. The researcher predicted that emergent themes would require clinical testing and/or some form of qualitative investigation. Therefore the researcher selected a mixed methods research (MMR) approach. In addition to this, the researcher selected a pragmatic worldview to support the research process. The selection of these will be discussed in subsequent sections.

4.4 Paradigms in Research

The researcher chose a pragmatist stance as the most apposite to address the research question. In this section the basis of choosing a stance is discussed and pragmatism is described in terms of its relevance to the research question. The researcher asserts that pragmatism is the natural partner to clinical research as its theoretical basis embraces pluralist methods/methodology. Further, this section will argue that foundational epistemology seeks an

unattainable theoretical starting point, in contrast to pragmatism which offers a practical starting point (Johnson & Onwuegbuzie, 2004).

4.4.1 Choice of paradigm

Crotty (1998) suggested a paradigm whereby social sciences research is constructed working from ontology through epistemology to methodology and finally to methods. Generally the epistemological stance is the main focus and is used to define the researcher's position. Broadly, there are many epistemological stances considered to exist on a spectrum with positivism at one end and constructivism at the other (Crotty, 1998). However, further reading indicated that this was just one of several views on the use of paradigms in research based on the work of Kuhn. In his original work, Kuhn was said to have used the term "paradigm" in as many as 20 ways (Morgan, 2007). This resulted in a lengthy clarification post-script to later editions. Morgan (2007) has summarised four basic types of paradigm in research which range from broad philosophical to specific method-based:

1. Paradigms as worldviews
2. Paradigms as epistemological stances/ metaphysical paradigm
3. Paradigms as shared beliefs in a research field
4. Paradigms as model examples (Morgan, 2007)

Morgan (2007) argued that the domination of paradigms as epistemological stances was a direct result of the proponents of qualitative research attempts to cast negative aspertions on quantitative research or more specifically research with a positivist grounding. Lincoln and Guba described, like Crotty, a "top-down" approach to research starting with an ontological position which then directs any subsequent epistemological assumptions (Lincoln & Guba, 1988). The key considerations for researcher methodologists became underlying

philosophical assumptions associated with differing ways of undertaking research. Additionally, concepts from the philosophy of knowledge were introduced that had hitherto been seldom discussed (Morgan, 2007).

It has been argued that this metaphysical paradigm has become exhausted and should be replaced with the third suggestion in the list above. This was proposed because despite the metaphysical paradigm's claim that methodological problems in social science research could be addressed through an ontology-driven version of the philosophy of knowledge, this belief system remains disconnected from practical decisions about the actual conduct of research (Morgan, 2007). It has also been intimated that there is no universal taxonomy for research metaphysics within the literature and that there are multiple typologies and definitions of epistemology, ontology and methodology and as such these models of knowledge are at best useful constructs (Scott & Briggs, 2009). Morgan stated that there are three basic anomalies existing in the metaphysical paradigm:

1. How to define paradigms
2. Whether those paradigms are incommensurate
3. The extent to which metaphysical assumptions actually guide research.

He raised the point that the first of these anomalies is controlled by human action and so who gets to choose and define the paradigms included on the list and what their purposes are by making those particular suggestions need to be considered (Morgan, 2007). While there has been this degree of human involvement, all definitions are, by definition, subjective. There has been no process of consensus. Pragmatism has no place on many lists.

With respect to incommensurability, the pragmatic refutation is to place an emphasis on shared meanings and joint action. That is, can two researchers

demonstrate that they understand each other and can they demonstrate this by working together on future projects? This is in stark contrast to the metaphysical paradigm's strong incommensurability stance that dismisses even the possibility of communication due to externally established boundaries (Morgan, 2007).

Finally, it has been noted that many researchers simply, in practice, do not start from the philosophy of social sciences as first principle, devoting little time to philosophical principles (Morgan, 2007; Robson, 2011b, 27). Philosopher Michel Foucault also disliked the idea of being associated with a specific school of thought potentially because it may have been too restrictive and might have limited his ability to "think freely" about social phenomena (Oliver, 2010b, p.88).

Having considered this argument, the researcher found the definition of a paradigm as a commitment to shared beliefs among a community of scholars the most appropriate for her study. This position received additional support from Scott and Briggs (2009) who argued that all knowledge is empirical and so there is no basis for foundational epistemology or ontology. Both Morgan, and Scott and Briggs suggested a pragmatist approach for overcoming the issues with the metaphysical paradigm. Knowledge begins with uncertainty and is inevitably based and framed by prior knowledge giving a research starting point that is practical and not wholly theoretical (Scott & Briggs, 2009).

The pragmatism advocated by the above authors focusses on the central tenets of the originators, such as "warranted assertions" (our judgements on an enquiry follow a process of investigation that are situated in life and to the world) and "workability" (usefulness and predictability). It requires one to give up the idea that a system external to the world would explain one's beliefs. Instead, using the Kuhnian shared beliefs paradigm, communities of like-minded scholars are found who have also considered the most important questions in

research: which questions are most important to study and which methods are appropriate for conducting those studies (Morgan, 2007).

4.4.2 What is Pragmatism?

Pragmatists want to “get on with the job” and are guided by practical matters and experience rather than by theoretical concepts (Robson, 2011b, 27). The focus is on research relevancy rather than academic philosophy. But how is pragmatism described? In Table 4.1, Robson working from Johnson and Onwuegbuzie (2004) described some of the features of pragmatism in the context of social research.

Table 4-1 Description of Pragmatism and the Pragmatic (Robson, 2011b, pp.28 - 29)

Seeks a middle ground between philosophical dogmatisms and scepticism.

Rejects traditional dualisms (e.g., rationalism vs. empiricism, facts vs. values) and generally prefers more moderate and common sense versions of philosophical dualisms based on how well they work on solving problems.

Recognises the existence and importance of the natural world or physical world as well as the emergent social and psychological world.

Places high regard for the reality of, and influence of, the inner world of human experience in action.

Knowledge is viewed as being both constructed and based on the reality of the world we experience and live in.

Endorses fallibilism (current beliefs and research conclusions are rarely, if ever, viewed as perfect, certain or absolute).

Justification of outcomes in the form of what Dewey called “warranted assertability” – judgements are assertable as long as they are not subject to doubt and have been derived from a systematic form of enquiry.

Theories are viewed instrumentally (they become true and are true to different degrees based on how well they currently work; workability is judged especially on the criteria of predictability and applicability).

Endorses eclecticism and pluralism (e.g. different, even conflicting theories and perspectives can be useful; observation, experience and experiments are all useful ways to gain an understanding of people and the world).

Human enquiry (i.e. what we do in our day-to-day lives as we interact with our environments) is viewed as being analogous to experimental and scientific enquiry. We all try out things to see what works, what solves problems, and what helps us survive.

Endorses a strong and practical empiricism as the path to determine what works.

Views current truth, meaning and knowledge as tentative and changing over time. What we obtain on a daily basis in research should be viewed as provisional truths.

Prefers action to philosophising (pragmatism is, in a sense, an anti-philosophy).

Takes an explicitly value-oriented approach to research that is derived from cultural values; specifically endorses shared values such as democracy, freedom, equality and progress.

Endorses practical theory (theory that informs effective practice).

Generally rejects reductionism (e.g. reducing culture, thoughts and beliefs to nothing more than neurobiological processes).

The central premise is that the meaning of a model, theory or idea is encompassed by its practical applications and so a pragmatist would advocate using whatever methodological or even philosophical approach that worked best for any given problem (Robson, 2011b, p.34). Moreover, warranted

assertions, a core pragmatist theory, are only derived from directed enquiry meaning that no a priori decisions about the nature of the social world are needed. Only statements derived from a research process can be warranted. The standards of the “warrant” are socially constructed and are variable across time, culture and value systems (Scott & Briggs, 2009).

Charles Sanders Peirce, considered the founder of pragmatism, described it as a method of “experimental mental reflection” generating theory in terms of conceivable positive and negative circumstances; a method allowing the generation of explanatory hypotheses (Peirce, 1878). One of Peirce’s achievements was that this way of thinking, from inference to explanatory hypotheses, was outside the usual foundational alternative between deductivist rationalism and inductivist empiricism (Hookway, 2010). This in plain language would be theory generation or theory verification.

It is the appropriateness of chosen research methods to answer the research question and hence the methodological approach rather than a commitment to an underlying philosophical doctrine which is described as the centre of pragmatism (Robson, 2011b, p.27).

Our influence over the study we perform is inherent in that we conceive the research question and we make choices of how it is investigated. These choices involve cultural, personal and social influences. This implies that, even with a pragmatist outlook, the researcher must remain reflexive in their approach; our values and politics are always a part of how we act (Morgan, 2007).

Physiotherapy follows a pragmatic pathway as opposed to a singular methodology. Healthcare involves situated enquiry starting with uncertainty as the patient subjectively describes their problem and moves towards warranted

assertions (via subjective discussion and / or objective testing) to an agreed treatment plan. In this way, clinical reasoning is not strictly hypothetico-deductive but is abductive in that it moves from inference to best explanation or put another way, initially converting observation into theories and then assessing those theories through action (Morgan, 2007). It combines approaches that would be considered incompatible if foundational epistemology and ontology approaches were adhered to. "Clinical reasoning seeks coherence" (Scott & Briggs, 2009). It seems logical therefore to the researcher that when seeking knowledge surrounding a group of patients, the same reasoning approaches should be taken but scaled up to a research design.

4.4.3 Criticisms of pragmatism

Criticisms of pragmatism in health research exist (Johnson & Onwuegbuzie, 2004). These include:

- Pragmatism cannot claim to offer access to the absolute truth only warranted assertions. Scott & Briggs (2009) presented the argument that pragmatists reject the concept of absolute truth based on foundational metaphysics as there is no Archimedean platform or inviolable knowledge from which it can be built, so this criticism is accepted but is considered irrelevant. Additionally, pragmatists do not try to represent reality. Rorty asserted that in **truth**, there is nothing very systematic or constructive to say about truth at all (Rorty, 1982).
- Judging solely by utility (of the theory) cannot exclude beliefs that are useful but false. Again, pragmatists may accept this but counter that people will act according to their perceptions anyway (Scott & Briggs, 2009).

- Warranted assertions are necessarily subject to revision as value judgments and human knowledge change. “Pragmatism is inherently provisional and approximate” (Scott & Briggs, 2009). Once more accepted but as the notion of absolute truth is rejected, the pragmatist would consider this inevitable. Analogous to this, Foucault viewed society as in a constant state of flux and highly complex. From this point of view, he felt that the need for a specific ideology or “fixed system of thought” was negated because the nature of truth is varying and is always subject to new thoughts and insights (Oliver, 2010c, p.140). And since a keystone of pragmatism is the understanding that we are fallible, we are never in a position to recognise that our beliefs about a subject are actually true—all we can say is that they meet standards of acceptance that are endorsed, for the time being, by our peers (Hookway, 2010).
- Pragmatism may give preference to applied research rather than basic sciences (Johnson & Onwuegbuzie, 2004). Pragmatism suggests that the research question should drive research processes, the most appropriate methodology and methods should be chosen which could very well be pure science based. So once again, this criticism is not in actuality a problem.

Lastly, it has been suggested that the concept of usefulness may be poorly defined (Johnson & Onwuegbuzie, 2004). Pragmatism views usefulness or workability in terms of predictability, applicability and how well something currently works (see Table 4.1). This should be addressed by the researcher and their choice of design in ensuring that the output contributes positively and rapidly to the knowledge base for their chosen area. For instance in this study

programme, the Delphi process (described fully in chapter 5) was the first consensus exercise of its kind in this area which demonstrated the panel's concurrence with the researcher that the pathogenesis of haemophilic arthropathy is multifactorial and further identified an extensive list of potential contributory factors. This was useful in many ways in that it provided the researcher with international support for their theory which translated into practical support. Potential contributory factors were raised that had not been considered previously by the researcher allowing an expansion of the research. It also enabled the researcher to develop an onward research plan encompassing many of the suggested factors. The second study presented within this document and fully described in Chapter 6, is a laboratory-based electromyography study of the activity of the gluteal muscles during the Star Excursion Balance Test. This was useful in that it enabled the researcher to streamline the execution of this test making it wholly applicable to the population under study and minimising the time required for research participants to attend. Furthermore, the results of this study are fully applicable outside the area of study as it was performed with healthy people. The researcher deems that these examples establish their pragmatic approach to ensure that the studies chosen for the Doctoral programme demonstrated workability.

4.4.4 Consideration of Alternative Approaches to Pragmatism

Musculoskeletal physiotherapeutic research has embraced evidenced based practice and the hierarchy of research in which qualitatively designed studies are deemed to possess the lowest strength of evidence and randomised controlled trials (RCTs) and meta-analyses thereof are deemed to have the highest. This trend has resulted in the conclusion that much of musculoskeletal

physiotherapy is without apparent “evidence” as RCTs fail to produce the results that are seen in every day practice. This may be due to the post-positive approach adopted of hypothesis testing, deductive reasoning, reductionism and empirical measurement (Creswell & Plano-Clark, 2007a, p.22). This process has resulted in documents epitomised by the NICE Early Management of Persistent Low Back Pain guidelines which recommend the sequential choice of a course of exercise, manual therapy or acupuncture (Savigny, Watson, & Underwood, 2009). These guidelines were developed following a process of literature search whereby the vast majority of evidence was RCT and meta-analysis based. Given the current climate in healthcare, it is apparent that the recommended approach is neither practical nor feasible on many levels. It is also one unrecognisable to clinicians who successfully treat the condition. The development of the guidelines does not mirror the clinical reasoning process used in health care but rather uses a theoretical concept of “truth”. The NICE guideline development process allows for expert consensus if RCTs are not available to address a study question, but do not merge expert opinion with RCT results. There is no place for social or cultural factors.

Constructivist approaches on the other hand, generate theory which is culturally and socially situated in the group under study. Knowledge is built inductively; theory is generated but not tested. This again would not have allowed the development of useable knowledge. In isolation, it gives in depth knowledge of the topic area but in theory cannot be generalised beyond the group. The researcher felt therefore that constructivist approaches could not contribute to the wholly practical aims of the study.

The researcher considered that both of these approaches would have limitations in trying to address the current research question. For instance, it

has been suggested that primary hypermobility could be a contributory factor to HA. A hypothesis could be developed to test for the presence of this in a cohort with HA using a post-positive reductionist approach. However, irrespective of the outcome, criticisms could be levelled at conclusions drawn in that it would be impossible to control or account for the effects of all the other potential influencing factors. Swinging to the other end of the scale, an interview study could have been determined upon which asked what influences a PWH's decision making when choosing exercise. Again, irrespective of the outcome, these results could not provide information amenable to a widely applicable practical solution. The usefulness of the qualitative results in isolation would have to be questioned. It would be more useful to take the interview results and derive further studies to look for correlations in a larger cohort. This may result in actionable outcomes. In isolation neither of these approaches was deemed appropriate and so the researcher therefore discarded them.

Another paradigm is critical realism. Like pragmatism, this view is said to offer researchers a middle ground between the opposing poles of the paradigmatic scale. It is said to value context-specific conditions whilst recognising that some perceived patterns are time and place contingent (DeForge & Shaw, 2012). Critical realism does indeed marry well with the researcher's working theory because it is mechanistically based. It recognises that problems under investigation are complex systems and not always amenable to hypothesis testing. Importantly it recognises that a mechanism can exist but not be active, be active but affected by other mechanisms, be active but not observed and hence provide unpredictable results. It rejects hypothesis testing as an arbiter of reality. As there is a recognition of the complexity of any given situation it allows for adaptations in research strategy that is, integration of qualitative and quantitative data (Scott & Briggs, 2009). Importantly, there is an emancipatory

aspect to critical realism with an aim to relieve subjects from the distress that they are under with the research position being driven with ontological considerations at the forefront (Scott & Briggs, 2009). Despite the apparent appeal of critical realism, it does depend on foundational epistemology/ontology which are concepts that the researcher has, on consideration, rejected as discussed above. For the pragmatist, consideration of ontological issues are limited to the acknowledgement that we have experiences (DeForge & Shaw, 2012) and their value lies in their relevance to a warranted assertion based upon them. So whilst aspects of critical realism can be embraced as per pragmatist rules, in particular the mechanistic approach, the researcher deems pragmatism the most apposite paradigm. This position is also endorsed in RWR approaches described in the next section.

4.4.5 Pragmatism fit with the Real World Research approach

Robson suggested that researchers take the practices of other researchers as reference points for the production of quality research as opposed to “maxims” handed down by philosophers (Robson, 2011b, p.27) that is, he endorses the shared beliefs paradigm and advocates a pragmatic approach. Pragmatism is so well suited for clinical research because it is problem-centred, pluralistic and real world practice oriented (Creswell & Plano-Clark, 2007a, p.22). Further as pragmatism is cited as centred on linking theory and practice (De Waal, 2005), it also supported the researcher’s aim of delivering clinically immediate output. One such pluralistic aspect is the adoption of aspects of realism in RWR and in particular using the mechanistic approach to research; looking for the how and why of an issue. Critical realists hope to come up with one or more postulated mechanisms which are capable of explaining a phenomenon and that have good support from research results and so there is reason to believe they exist.

This is reflected in the conceptual framework discussed in 4.2 which reflects one aspect, known as Generative Causation, which is where the cause of event B following event A is due to the operation of one or more mechanisms (Robson, 2011b, p.32).

4.5 Mixed Methods Research

Having identified the basis of the research project, the methodology naturally suggested applying multiple methods in order to address both the overarching and subsidiary research questions. This could be achieved using Mixed Methods Research, Multiple-Method Research or potentially Bricolage.

Definitions for these varying forms of research design vary from expert to expert leading to some confusion for the researcher in defining the project. It has been suggested that a project cannot be defined as MMR if the studies conducted are capable of standing alone (Morse, 1991). However, Creswell and Plano-Clark (2011) do not concur with this view producing the following criteria for MMR:

1. Collects and analyses persuasively and rigorously both qualitative and quantitative data (based on the research questions)
2. Mixes (or integrates or links) the two forms of data concurrently by combining them (or merging them), sequentially by having one build on the other, or embedding them one within the other
3. Gives priority to one or both to both forms of data (in terms of what the researcher emphasises)
4. Uses these procedures in a single study or in multiple phases of a programme of study
5. Frames these procedures within philosophical worldviews and theoretical

lenses

6. Combines the procedures into specific research designs that direct the plan for conducting the study. (Creswell & Plano-Clark, 2011)

An alternative is an approach known as Bricolage which is derived from qualitative critical theories and so might tie in with the aspects of critical realism that the researcher intended to apply to this project. Bricolage involves the process of employing (qualitative) methodological processes as they are needed in the developing context of the research situation. The interdisciplinary feature is central but a coherent theoretical stance must be maintained. The *bricoleur* views research methods actively rather than passively implying that we should actively construct our research methods from tools at hand rather than passively receiving the “correct” universally applicable methodologies. They also try to ensure that their approaches are driven by the specific demands of the enquiry at hand (Kincheloe, McLaren, & Steinberg, 2011). However, the researcher has not seen this approach applied to the collection of qualitative and quantitative data types. Additionally, the researcher had rejected the metaphysical paradigm approach to research in favour of the shared beliefs paradigm, so whilst this approach held many appealing elements, it would be difficult to adhere to the required metaphysics. Therefore on reflection, the researcher has chosen to define this project as MMR as it meets the criteria proposed by Creswell and Plano-Clark. It could be argued that the qualitative element is somewhat lacking in that collected data were neither exhaustive nor rich however, but it meets their suggested requirements.

To support definitions, rationales have been developed for the use of MMR by Greene et al. (1989) and Bryman (2006) from which the following are applicable to this study:

- **Development** (Greene, Caracelli, & Graham, 1989). An initial exploratory phase was required to guide and develop the rest of the study programme.
- Main study was used to **confirm and discover** (Bryman, 2006). Having developed theory from the exploratory data, the (mainly) quantitative study was used to both explore and investigate further.
- **Complementarity** (Greene, et al., 1989)/ **Completeness of account** (Bryman, 2006). Certain sub-questions generated at the exploratory phase were best addressed by mixing quantitative and qualitative methods within one study where one data type enhanced the findings of the other.
- **Triangulation** (Greene, et al., 1989)/ **Enhancement of results** (Bryman, 2006). Multiple quantitative testing was used to corroborate certain findings.

MMR is considered a creative and unrestrained form of research (Johnson & Onwuegbuzie, 2004). Overall taking a mixed approach allows the researcher to mix and match design components providing the best chance of satisfying their research question and so be able to produce results that are useful and beneficial to the population under study however it is not without its critics, and this will be discussed along with the origins of the practice in the next section.

4.5.1 Origins and Challenges of Mixed Method Research

Jick (1979) cited Campbell and Fisk from 1959 who are credited with originating the concept of using more than one quantitative method to validate a process to ensure that any variance in the measured variable reflected that of the trait and not of the method, thereby enhancing the validity of results and reducing the

likelihood of a methodological error being responsible for the outcome. This triangulation is described as the use of differing methodologies to investigate the same phenomenon (Jick, 1979). Later, Morse (1991) added further refinement to the process with the delineation of sequential and simultaneous triangulation. The term "methodological triangulation" was used to describe the process (Morse, 1991). Other terms such as "integrated" and "mixed methodology" have also been used until the term mixed methods research took prominence following publication of the 2003 book: "Handbook of Mixed Methods in Social and Behavioural Research" (Creswell & Plano-Clark, 2007b, p.6). The concept of associating a specific method with a specific metaphysical paradigm is endemic, but it has been argued that this linkage is neither necessary nor warranted (Howe, 1988). However, because of this association the design did not gain any prominence until the 1990s after a period known as the "Paradigm Wars" where purist proponents of quantitative and qualitative research debated the relative superiority of each at determining the truth for any given research question. It was argued that mixing paradigms with incommensurable epistemic and ontologic foundations creates incoherence; that the abstract paradigm should determine research methods in a linear fashion. There was a "relentless focus on the differences between the two orientations" (Johnson & Onwuegbuzie, 2004, p.14). For each paradigm there was and remains for the purists, a claim to superiority based on the richness and observability of the data for qualitative and generalisable, hard data for the quantitative (Johnson & Onwuegbuzie, 2004). These purists continue to assert that mixing of methods cannot occur based on foundational paradigmatic principles. This is known as the "Incompatibility Thesis".

From pragmatist view point however, widening acceptance of practice is noted and many researchers find a practical value, therefore the "Incompatibility

Thesis” is not a warranted assertion (Scott & Briggs, 2009). Finally, the argument is considered spurious as pragmatists reject the foundational claim of epistemology (Scott & Briggs, 2009).

From an alternative perspective, it is also suggested that the debate is based on the premise that epistemology and methods are synonymous. This is countered by the argument that epistemology does not dictate the specific data collection or analysis methods that a researcher must use for specific problems (Johnson & Onwuegbuzie, 2004). Howe (1988) underpinned this position by pointing out that methods or what he terms “logics in use” are actually what drives research, determining what will work best to answer a research question and that epistemology (reconstructed logic) needs to move towards that.

No matter the orientation of the researcher, all research at its most basic is attempting to do the same thing: to provide “warranted assertions” about human beings (Johnson & Onwuegbuzie, 2004). MMR acknowledges the merits of both research choices and tries to utilise the strengths of each whilst ameliorating their weaknesses, however debate continues.

Continuing to define MMR appears necessary as a way of potentially adding some rigor to the process in order to improve its credibility amongst naysayers. While defining it too tightly may also act to restrict its flexibility if say, the “specific research designs” (item 6 in the criteria of Creswell and Plano-Clark above) are taken by researchers as the only acceptable ones. One of the benefits of MMR is its responsiveness to data as it is gathered allowing the RWR researcher to adjust methods and even direction (research questions) in order to, in this case, achieve the aim of improving the chances of young people with haemophilia’s not developing HA. In conclusion, as succinctly put by Johnson and Onwuegbuzie (2004): “Mixed methods research offers great

promise for practising researchers who would like to see methodologists describe and develop techniques that are closer to what researchers actually use in practice” (Johnson & Onwuegbuzie, 2004, p.15). Typologies of MMR put into practice for the current study is described below.

4.5.2 Study Design

Typologies of design are proposed by several authors such as Creswell, Johnson, Onwuegbuzie and others using timing (sequential versus concurrent), weighting (qualitative versus quantitative) and integration (of data) for categorisation. The use of typologies in MMR has become quite formalised and is said to convey a sense of rigour, providing guidance to what the researcher intends to do. However the use of typology implies a priori commitment to a design type and outcomes of MMR are not always predictable (Bryman, 2006). Bryman (2006) considered these typologies almost too refined as they are largely theoretically constructed and not obviously influenced systematically by examples of MMR. The researcher considered this especially so in health research as many typologies were developed for use in other fields such as education and may not be reflective of researcher practice. Indeed typologies proposed by Creswell and Plano-Clark (2011) were immediately met with feedback from active researchers pointing out that these were not fully inclusive of their successful practices. Creswell later suggested a reconceptualisation of designs away from typologies to other ways of thinking with no need to weight the qualitative and quantitative elements (Creswell, 2010). Indeed, using an MMR design involves approaching the research in a “cyclical, recursive and interactional” way (Johnson & Onwuegbuzie, 2004, p.21). The researcher’s application of MMR principles to the overarching research question for this study: “In what ways do non-haematological factors contribute to ankle

arthropathy in people with haemophilia and how can these factors be identified?” - are now described in terms of timing of phases, weighting and data integration, expanded upon in subsequent sections.

4.5.2.1 Design overview

Using the published typologies for ease, this project could be said, in terms of timing and weighting, to be an example of a quantitatively-weighted, sequential exploratory design. The study design is presented in Figure 4.2.

In this design the results of an initial qualitative section determine the structure and more importantly the direction of a quantitative section. This was required because there is a dearth of published literature regarding the potential for non-haematological factors to influence HA development and so there was no established platform from which to design the studies to investigate the problem. Data were connected from the initial exploratory phase to a main case-control study in order to guide and develop the theory for its purpose and design. This fits with RWR where theory must be gradually and carefully built up so that investigations can eventually be done that will clarify the extant mechanisms in play (Robson, 2011b, p.34). Within the final main study data were merged as operating within a mechanistically-enhanced pragmatic way indicated the need to consider as many potential influencing factors in one “go” in order to produce a more real-world picture when data analysis were undertaken and results were interpreted. This overall design will now be discussed in greater detail.

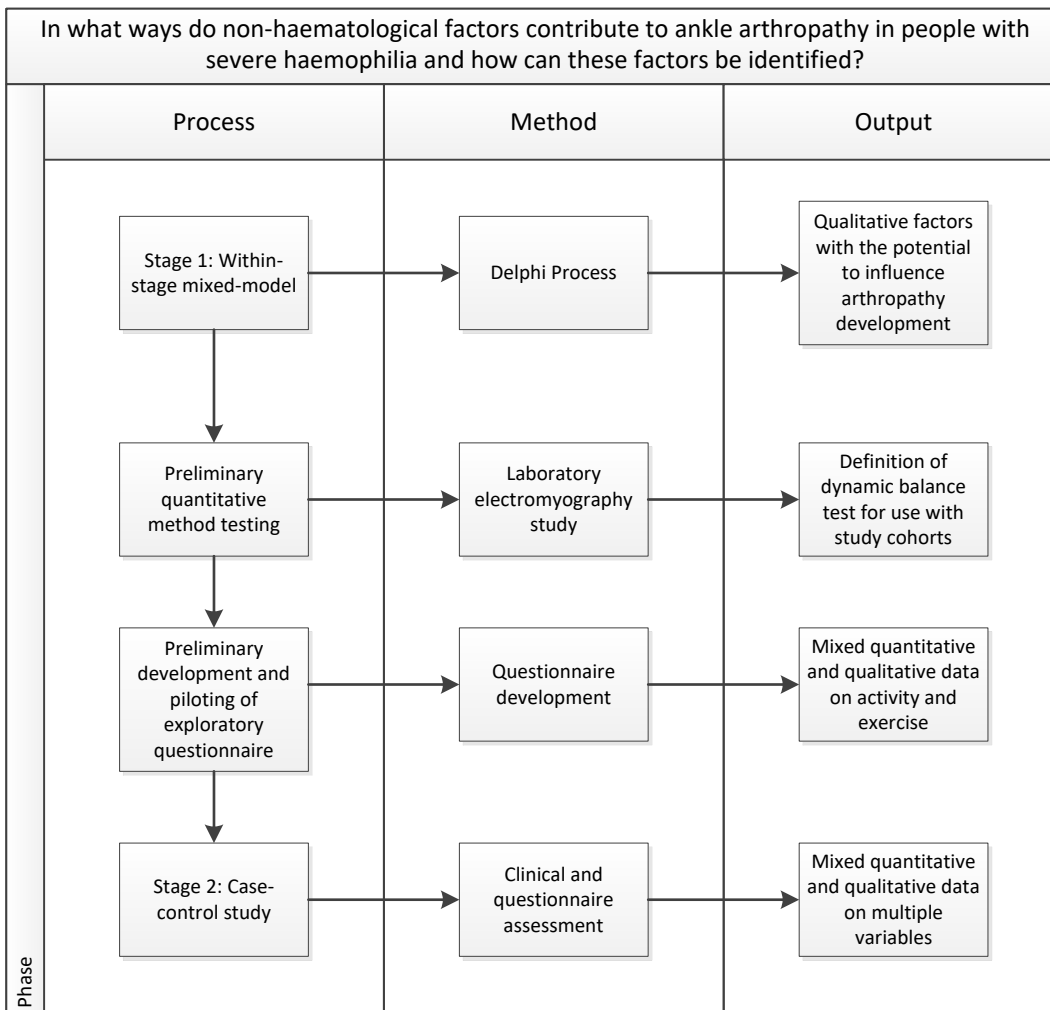


Figure 4-2 Overall Study Design

4.5.2.2 Timing

This study is sequential, but it is also a hybrid in that it has elements in which qualitative and quantitative data were collected concurrently. This occurred both as an initial choice and in response to direction from the Delphi Process. The concurrent data collection elements, the initial Delphi Process and later exploratory activity and exercise questionnaire, constitute within-stage mixed model designs utilising both open and closed question types for data collection (Johnson & Onwuegbuzie, 2004). This view of the practice is supported by an analysis of how 232 social science MMR studies were undertaken which found

that 27% had used a single instrument to collect the quantitative and qualitative data (Bryman, 2006).

4.5.2.3 Weighting

Descriptions of MMR usually state that both quantitative and qualitative data must be collected and that one type is considered dominant. The researcher is aware that the qualitative elements of this study are lesser and that the quantitative data were dominant. The use of the single stage questionnaires collecting both open and closed ended information, which constitute the qualitative element, is recognised as a “grey area” by Creswell whilst acknowledging that this still meets their criteria for defining a study as MMR (Creswell & Plano-Clark, 2007b, p.11).

4.5.2.4 Data integration

Three ways of handling data are noted in the literature: merging, connecting and embedding (Creswell & Plano-Clark, 2007b, p.7). Here, data were connected in that the first phase data were used to inform the structure and data collection methods of the second. However, the within-stage mixed model sections, the Delphi Process and the exploratory activity questionnaire, also merge data. What it means to integrate findings in MMR remains an area of discussion (Bryman, 2006). Three levels of integration or merging have however been proposed:

1. “two-phase design” –phenomenon studied in separate stages using techniques conventionally associated with each paradigm
2. “dominant-less-dominant design” – study presented with a single dominant paradigm but within that framework methods are borrowed from the other paradigm to answer a single research query

3. “mixed methodology design” – working backwards and forwards between inductive and deductive models of thinking. Mixing aspects of both paradigms at all or many methodological steps. (Creswell, 1994)

The researcher considers that this current project is a “mixed methodology design”. In this programme an initial (partly) qualitative exploration is followed by (dominantly) quantitative assessment, neither phase is purely within one paradigm and so does not meet the definition for “two-phase design”.

4.6 Consolidation and Conclusion

Birks and Mills (2011) described a situation of methodological congruence that they believe occurs in good research practice which happens when there is harmony between:

1. The personal philosophy of researcher,
2. The research aims,
3. The methodological approach chosen to address aims (Birks & Mills, 2011).

Considering the information presented in the preceding sections, the researcher considers that she has shown that pragmatism with a mechanistic slant coupled with MMR was ideal to address the research aims. In order to summarise and consolidate the researcher’s study plan, she has presented the overall programme using terms proposed by Robson (2011) who suggested planning research in terms of purpose, conceptual framework, methods, and sampling strategy which all lead to the research question. This is illustrated in Figure 4.4, and detail for each of the studies involved can be found in Chapters 5, 6, 8 and 9. It is this process that allowed the researcher to produce outputs that are directly clinically applicable, allowing swift translation into practice.

Pragmatism has supported the choices described above, the process being driven by the research question and a desire to produce results that can be used for effective practice. The first application of pragmatic principles is described in the next chapter in which the first study is described in terms of the chosen method, the procedure, results, discussion and application.

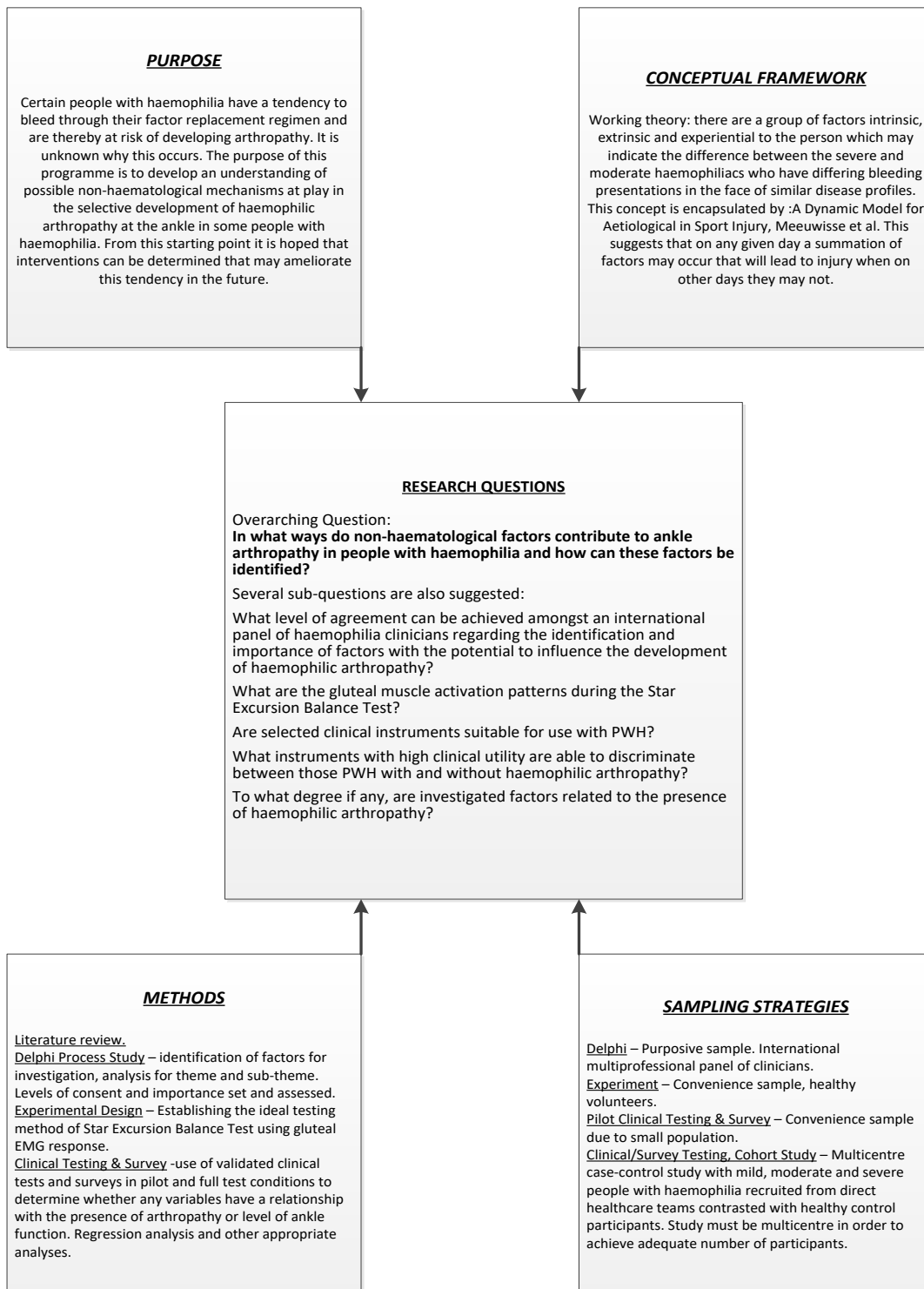


Figure 4-3 Framework for Research Design

Chapter 5 A Delphi Consensus Exercise on Potential Contributory Factors for the Development of Haemophilic Arthropathy of the Ankle

5.1 Introduction

The current research data regarding the development of HA provide a minimal amount of specific research evidence to enhance clinical practice. A first body of evidence (discussed in Chapter 2) was based on biochemical mechanisms for the pathogenesis of HA based on blood within a joint. The translation of this experimental research work into clinically applicable information is not, on the whole, easy. Additionally, it could be argued that biochemistry in isolation cannot wholly explain the clinical picture.

A second body of evidence (partly discussed in Chapter 3) investigated specific interventions such as heel supports and splinting (Buzzard & Heim, 1995; Seuser, et al., 1997) and gait analysis (Bladen, et al., 2007; Lobet et al., 2010; McLaughlin, et al., 2010; Stephensen, 2008) in PWH with already developed arthropathy, or joints with established bleeding tendency. This body of work, while producing evidence useful to manage patients, does not contribute to a deeper understanding of the pathogenesis process in order to identify effective preventative measures.

In order to begin the process of identifying effective preventative interventions, the researcher considered that it would be beneficial to formally elicit beliefs on the clinical aspects of the development of HA at the ankle which would add value to, clarify, complement and direct the current research programme. The researcher considered a semi-structured Delphi process apposite for understanding the putative role for factors that influence the development of HA.

The purpose of this chapter is to describe the rationale for the choice of survey method and describe the study design used. The study procedure, results and findings are presented and these findings are discussed, along with an evaluation of the process. Finally, the rationale for the choice of factors selected for onward study is presented.

It should be noted that throughout the literature the terms Delphi, Delphi - Method, - Technique, - Survey, and - Process are used interchangeably, in this Chapter the simple term Delphi will be used. Additionally, those taking part have been referred to as respondents, participants or panellists, the latter of which will be used.

5.1.1 What is Delphi?

A classic Delphi uses a semi-structured survey given to a pre-selected panel of experts who are asked to provide their opinion anonymously on a subject area. These data are then collated by a facilitator and fed back to the panel who then order or rate the data in some way. These ratings are again collated and re-distributed. Panellists are asked to review their rating in light of group opinion. The process iterates until the desired levels of consensus set by the investigators are obtained, and once that is achieved the process is deemed complete. Usually a minimum score is set as cut off to deem a statement important, and a consensus level is used to indicate the amount of agreement expressed by the panel on each statement. Hasson et al. (2000) described it succinctly as "an iterative multistage process designed to combine opinion into group consensus" (Hasson, Keeney, & McKenna, 2000).

A recent Medline search using the terms "Delphi" and process, study, method or survey resulted in 3198 hits starting from the year 2000 indicating a general acceptance of the technique in health research. Uses included developing

research priorities (Rankin et al., 2012; Rushton & Moore, 2010), clinical standards (Hardy et al., 2004), clinical practice guidelines (Hunter et al., 2011) and training priorities (Duffield, 1993).

5.2 Rationale for using Delphi

The rationale for using Delphi has been cited as achieving a consensus of expert opinion on any given topic where it is considered that there is too much or too little information, uncertainty or contradictory information in the area under investigation (Hardy, et al., 2004; Hicks, 2009a; Mead & Moseley, 2001). More explicitly, Delbecq et al. (1975) recommended it as a method of group interaction for numerous reasons which, for the purposes of this study included:

- Multiple judgements in the context of a complex problem where there is no apparent acceptable solution to all parties
- Ideas generation and evaluation
- Group interaction that is not face-to-face, and so constrained by time or finance
- Structured group interaction irrespective of group size or membership, allowing for all personality types to contribute equally
- Correlation of informed judgements across a range of disciplines on a specific topic
- The possibility of (*quasi*) anonymity of group respondents (Delbecq, van den Ven, & Gustafson, 1975)

The italicised *quasi* in the last point above was added by the researcher, as anonymity in Delphi is worth further comment. The nature of the survey is such that responses cannot be identified or linked to any individual, however, the researcher has the task of inviting the panel and it is impossible for them to be unaware of their identity. So whilst the panel cannot be called truly anonymous,

the data that it generates can. Panel anonymity can be improved by having the survey administered by a research assistant who will have no part to play in the analysis and onward utilisation of the generated data. This means that other than preparing the survey and initial list of panellists, the researcher would be blinded; and this option was taken in the application of this study.

Considering the advantages in the bulleted list above, the appeal in healthcare situations is evident, where calling time-pressured clinical staff to meetings to discuss non-essential topics may be seen as an imposition. Moreover, the geographical diversity of the haemophilia clinical community is such that a remote-access method of engagement was required. With a multi-discipline panel invited, the researcher believed that it would give voice to those who may not have spoken up in face-to-face situations. It could also be said that in accessing a larger and wider ranging group for the panel, the researcher had also successfully networked and stimulated their interest in the subject area. This may establish good will for future collaborative work, developing some ownership of the overall research programme results for acceptance and integration into practice. Finally, it has been suggested that information gained via experts in a Delphi panel has high content and concurrent validity (Baker, Lovell, & Harris, 2006). The researcher therefore determined that Delphi was the ideal first stage platform for this research programme.

5.2.1 Study Aim

The aim of this Delphi process was to understand the opinion of a group of experts on what they believe influences the development of HA.

5.2.2 Study Objective

The **primary objective** was to generate ideas for potential factors that are

believed to contribute or influence the development of HA of the ankle and rate these factors in terms of their perceived importance to HA development. The **secondary objective** of the study was to use the suggested factors to guide the next stages of this research programme.

5.2.3 Primary Endpoint

The study was concluded when the set levels of agreement and consensus had been met on the questioned factors.

5.3 Study Method Considerations

5.3.1 Design of the Survey

It has been suggested that the usefulness of Delphi is only limited by the imagination and skill of the person designing the survey (Linstone & Turoff, 1974) and as such its structure can be carefully adapted with both qualitative and quantitative aspects to best achieve a useful outcome. A Delphi constitutes a within-stage mixed model design (Johnson & Onwuegbuzie, 2004) as the responses to open ended questions allow analysis of more subtle opinion, garnering a fuller understanding and clarification of the panellists' view.

The choice of specific Delphi structure is predicated on the way in which the factors to be rated are to be obtained. In theory, the survey structure should encourage/allow the panellists to fully explore the research question thereby averting the potential problem of lack of in depth data with the caveat that the design cannot control for panellists who choose not to go into detail. One way of offering panellists the opportunity to explore a problem is to allow free prose responses. This does raise a risk of the facilitators being unable to glean meaning from the responses. Or as Jones puts it a "danger of deriving collective

ignorance rather than wisdom" (Jones & Hunter, 1995, p.3). This can reduce the validity of the study and additionally make on-going rounds difficult to structure (Hardy, et al., 2004).

It has therefore been argued that the problem be explored on behalf of the panel in the first instance, providing panellists with the factors to be rated as the first round and that this may result in more valid and reliable responses.

However, it must be ensured that the information has been derived in a systematic manner (Hardy, et al., 2004) and doing so in this study would have raised all of the issues of working with a geographically diverse healthcare group. This Delphi structure often occurs and is generally described as "modified". It would also appear to create a new risk of discounting potentially enlightening information unless the survey design allows panellists to submit additional opinion at some point.

The research aim for this study encompassed discovering what factors experts in haemophilia believed could influence HA development, and so a modified structure without an ideas generation round was precluded. However, during the rating rounds in a classically-structured survey, the panel is presented with identical information in each round and is asked to order and reflect on their ordering, but for this study, the structure of the rating rounds was modified on the advice of a statistician to reflect the strength of consensus on the incoming data. Therefore, the design of this survey is a modified classic structure.

Other considerations in Delphi have been divided into four areas: panel composition, participant motivation, importance and consensus, and feedback (Hardy, et al., 2004). The following sections will describe their application to this study.

5.3.2 Panel composition

Two panels were to be recruited; one consisting of clinicians and another of PWH and carers. Two surveys were felt necessary in order to ensure appropriate language was used on each. A review of panel size has suggested that a panel of 20 is sufficient. It was stated that larger panels appear to have higher drop-out rates whilst those of around 20 appeared to retain their members (Mullen, 2003). Keeney et al. (2001) felt that the panel size should be dependent on the purpose of the study, project design and time frame for data collection (Keeney, Hasson, & McKenna, 2001). But it has also been stated that when the research question is a matter of determining priorities, large participation groups result in more reliable results (Hardy, et al., 2004). Therefore the researcher chose to invite large panels in order that, even with a marked drop out of panellists, it was likely that 20 would be retained.

The second panel was to use PWH and/or carers as the source of expert information. There is an argument that information provided by patients on a technical subject cannot be as valuable or valid as that provided by professionals (Baker, et al., 2006) but it is the opinion of the researcher that this may be a reflection on the facilitator's philosophy and perhaps ability to value and interpret the information. PWH do have unique experience or knowledge of their condition that cannot be equalled by professionals. The researcher considered that if the Delphi was to provide a consensus in which a wide variety of people had confidence then it would appear valuable to use panels of varied background.

Using experts as Delphi panellists is cited as a major failing by Sackman (1974) as the definition of what is meant by the term is not clear. Keeney et al. (2001) noted a wide range of definitions of expert which included "informed individual"

and "specialist in the field". In the current study after reviewing the literature, a broad definition of expert was taken, which was:

- Any PWH with isolated or dominant ankle arthropathy
- A carer or guardian with an understanding of the factors that might contribute to HA
- Clinicians across different specialties who either understand the factors that could contribute to HA or see PWH with HA

5.3.3 Participant Motivation

Fatigue of panellists is described in terms of the length of the process which can result in the loss of motivation and failure to complete the study (Duffield, 1993; Fink et al., 1984). Strategies suggested to reduce drop-out are: obtaining participants' written consent to participate in all rounds (Hardy, et al., 2004), careful survey design and layout, in particular question clarity (Duffield, 1993), and sending out reminders between rounds (Hasson, et al., 2000). The researcher implemented all of these motivational aids and in particular sought expert assistance in the design and build of the survey.

5.3.4 Importance and Consensus Levels

The determination of how consensus is reached has been described as a major deficiency of Delphi (Duffield, 1993). As yet, there are no widely accepted methods described for assigning importance to results and determining consensus (Hardy, et al., 2004). The researcher considers that the selection of these points should be determined by the purpose of the Delphi. For instance, development of clinical guidelines should require a higher importance and stronger consensus level than those for selecting research priorities.

5.3.4.1 Assigning importance

Assigning importance refers to the point at which a researcher decides to retain an item for inclusion in subsequent rounds and the final outcome. The choices for assigning importance are to either rank or rate the items and then to assign a cut-off point. The methods in the literature are very varied. A popular ranking system asks panellists to number order the items and then a certain number are retained (e.g. (Skews et al., 2000)). On deliberation, the researcher felt that a rank ordering process may have resulted in a poorer outcome as it may have resulted in panellist drop-out due to not feeling able to distinguish between items adequately (they may feel more than one item deserves the same attention), and the increased time this kind of deliberation would take.

Therefore the researcher chose a rating system using a Likert scale which is also commonly found in the literature in various forms, using this, a point is selected at which the response is considered positive (Duffield, 1993).

However, in order to ensure panellists did not equivocate in their responses the researcher chose an even 6 – point scale (1 being “not at all important” and 6 being “extremely important”) where items marked with a score of four or greater were considered important for onward study. This is in keeping with the research study’s underlying theory that individual factors may not influence HA development but may do so when interacting with others, and so factors considered only moderately important could be actually be significant.

5.3.4.2 Determining consensus

How to determine that consensus has been reached by these methods remains under discussion in the literature. Where a Likert scale has been selected, differing methods of determining consensus are found. The simplest method is to select a point and tally how many have voted for it - usually presented as a

percentage value. Others use a more complex interpretation on the scale such as McDonnell et al. (1996) who used a 9-point scale and then bracketed responses into 3-point divisions (1-3, 4-6, 7-9). Agreement was considered to have occurred if 75% respondents placed their mark in one of the divisions (McDonnell et al., 1996). The validity of selecting a percentage of panellists agreeing on an item as a measure of consensus has been questioned and the stability of the response through a series of rounds has been proposed as a more reliable indicator (Crisp et al., 1999). Stability is defined in this instance as the motion (or lack thereof) of items above or below a selected point. For instance, Rushton and Moore (2010) selected the point at which less than 30% of items were moving above or below the level of importance (Rushton & Moore, 2010). The researcher considered that the method chosen could also reflect the purpose of the Delphi. A study requiring agreement on clinical guidelines needs to ensure results have stability of opinion if they are to be adopted and implemented, whereas one examining opinion on investigative topics such as carried out here, can achieve acceptable results with simple percentage agreement which was therefore chosen. A review of the literature indicated that studies with a similar purpose (e.g. (Rankin, et al., 2012)) had chosen 60% and so the researcher concurred with this level.

5.3.5 Feedback

After the second round in a classic Delphi, group opinion is collated by the facilitator and some form of feedback is provided to participants in the third round in order to allow them to consider their stances in relation to group opinion. Feedback can take the form of a summary of collated responses or examples of individual responses (Hardy, et al., 2004). This introduction of material selected by the facilitator needs to be managed with care as it is a

potential source of bias. In order to avoid this, in this study, the panel was provided with the rating in graphical form with the percentage voting included with no further written comment.

Determining how feedback was to be managed concluded the survey design considerations and so to summarise, a Delphi using the following format was used:

- A classic modified structure in which ideas were first generated and then rated with a Likert scale
- The survey was built and administered by the host NHS trust web manager using Survey Monkey (SurveyMonkey.com LLC, California, USA)
- Two panels; one clinical and one PWH were to be recruited
- Written consent was obtained with survey participation
- Reminders were used to encourage completion
- Importance was set at a score of 4 or greater on a 6-point Likert scale
- Consensus was set at 60% of panellists agreeing, that is:
 - 60% or more of panellists placing their vote in 4 - 6 on the Likert scale, retained the factor for future consideration
 - 60% or more of panellists placing their vote from 1 – 3 on the Likert scale, discarded the factor
 - Factors not gaining a 60% vote had not reached consensus

The Delphi was then implemented as described below.

5.4 Procedure

The Delphi designed by the researcher was tested for clarity of language and

face validity by a consultant haematologist, physiotherapy academic, clinical specialist physiotherapist and a lay person. They agreed that both were in place. Ethical approval for the study was gained through the appropriate NHS and University of Brighton research ethics and governance committees (See Appendix 1). The study protocol and funding letters are attached as e-Appendices 1–3 and Round 2 of the Delphi is found in Appendix 2 with Round 1 and 3 in e-Appendices 4-5 (A list of e-Appendices can be found at the end of the appendices section).

5.4.1 Recruitment

Firstly, a list of clinicians (medical consultants, physiotherapists, nurses and podiatrists) from many countries, derived pragmatically as those across a range of specialties considered able to contribute to the research question (haemophilia, musculoskeletal medicine, rehabilitation) and likely to be responsive to an email approach, was assembled. This latter criterion was determined through personal knowledge of the host haemophilia centre staff. The researcher attempted to recruit a second panel of PWH, family and carers following advice from The Haemophilia Society by utilising their social media presence and advertising on their Facebook page. During the same period direct approaches to PWH were made by the healthcare team in clinic.

The survey was carried out electronically and the host NHS trust web manager administered it. This means that nominated potential panellists were recorded on a central database held securely outside of the research team. An email invitation and information sheet which included the rationale for the study and for the panellists' inclusion was sent to prospective panellists. Clinical participants were informed that they could discuss their responses with

colleagues or other interested parties and provide an enhanced group response.

5.4.2 Round 1: Ideas Generation

Round 1 requested the panellists to provide up to ten factors that might influence the development of HA at the ankle together with rationales for the suggestions. The researcher considered that, owing to the heterogeneity of the panel, some panellists might feel better able to respond if given some background data and so this was provided in terms of a review article about HA and also an article about the Delphi process. Panellists were requested to feedback on the ease with which they had provided the factors and rationales and were offered a final open comments box. This was included in order gain improved insight into the participants' decision-making. An example of raw data is included electronically as eAppendix 6. The panel were given a four week period to complete the survey and were sent a reminder after two weeks.

The potential factors suggested underwent content analysis to identify themes and sub-themes with no reference to any specific theoretical stance (Robson, 2011a). Where factors were suggested of very similar themes, an umbrella title was assigned. Each factor was supported by examples of panellists' quotations. Results were then reviewed and approved by supervisors and advisors.

5.4.3 Round 2: Initial Rating

Rating of the suggested factors began in Round 2. Items generated were listed in their categories and were presented with a request that panellists indicate how important they felt the factor influenced the development of ankle HA on the Likert scale. An open feedback box was also included for comments on clarity, proposing of additional factors or general feedback. Again the panellists

were given four weeks and were sent reminders after two weeks.

5.4.4 Round 3: Final Rating

As consensus was not achieved on all items after Round 2 a third round was required. On the advice of a statistician factors put forward were those that did not reach consensus in Round 2, those that were borderline, new suggestions and those where there were requests for clarification. Additionally, in order to try to achieve full consensus in this round a different style of rating was chosen following discussion with the statistician. A definitive-outcome motivated scoring system was used where a dichotomous choice was given, in this case panellists were provided with the previous rating position in graphical form and were asked whether the factor should be kept in or left out of future consideration (lorio, 2013). Panellists were finally asked an open question regarding the participation in a Delphi study. The research team decided that owing to time constraints for the project and panellist motivation for a fourth round, factors without consensus at the end of Round 3 would be deliberated upon by the research team to decide their fate. The same response period and reminder were used for the final round.

5.5 Results

5.5.1 Round 1

One hundred and eight participants were invited to participate and fifty consented however, 39 clinicians from 11 countries fully completed the study giving an initial response rate of 36%. Table 5.2 presents an overview of the expert clinician panellists. A total of 280 suggestions were generated from this panel. Following thematic analysis, these were divided into four categories:

- Factors intrinsic to the PWH relating to the musculoskeletal (MSK)

system

- Factors extrinsic to the PWH affecting their physical health
- Factors relating to treatment compliance, education and non-haematological treatment
- Factors relating to the underlying haematology and its management

Of the 280 factors, the vast majority, 151 (54%), were in the intrinsic MSK category whereas the least were in the haematology-related category. The intrinsic MSK suggestions outstripped the other remaining categories at a rate of between 2.8 - 4.6 to 1. Thematic analysis led to the creation of forty-five factors under the four categories. The title of the factor was determined by the researcher but the description of the factor was formed from the panellists' own words thereby minimising researcher influence. The factors and their accompanying rationale can be found in Appendix 3. The final factor list is presented in Figures 5.1 – 5.4 along with their Round 2 scoring also.

Recruitment of PWHs/family/carers proved difficult and only three data sets were received in Round 1. Review of these data did indicate that the themes were of a similar nature to those suggested by the clinician panel but it was felt that this was not a sufficient body of data to include in the analysis.

Table 5-1 Demographics of Panel. Note some questions were multi-response

Professional Background	Count	Country of practice	Count	Specialty Areas	Count	Years of Practice in Specialty	Count
Consultant (medical)	17	United Kingdom	1	Haemophilia, Haemostasis and thrombosis	39	1 - 5	9
Consultant (physiotherapist)	4	Australia	1	Trauma and Orthopaedics	5	6 - 10	8
Consultant (nurse)	2	Belgium	1	Rheumatology	3	11 - 15	5
Consultant (podiatrist)	1	Brazil	1	Physiatry/Rehab. medicine	3	16 - 20	6
Consultant (other)	1	Canada	5	Musculoskeletal	11	21 - 25	8
Clinical Specialist (physiotherapist)	9	Croatia/Hrvatska	1	Foot and Ankle	6	More than 25	12
Clinical Specialist (nurse)	1	Malta	1	Connective Tissue Disorders	0		
Clinical Specialist (other)	0	New Zealand	1	Other	3		
Physiotherapist	15	Spain	1				
Nurse	1	Turkey	1				
Occupational Therapist	0	United States	5				
Podiatrist	1						
Researcher	5						
Academic	6						
Paediatric PWH population	7						
Adult PWH population	5						

5.5.2 Round 2

The fifty panellists who had initially consented to complete all three Rounds, plus 6 others who had expressed their disappointment at missing the Round 1 deadline were invited to participate in Round 2 (panel anonymity precluded determining who of the original 50 had completed the survey). One invitee actively declined to take further part citing perceived lack of expertise resulting in an invited panel of fifty-five. 37 out of 55 or 67% completed all questions. Figures 5.1 – 5.4 show the voting in each of the four categories. Six items did not reach consensus and four were considered borderline either above or below the consensus level. Clarity was requested by panellists on two items. One factor reached a consensus for rejections which was “cigarette smoking” and all others reached consensus for retention.

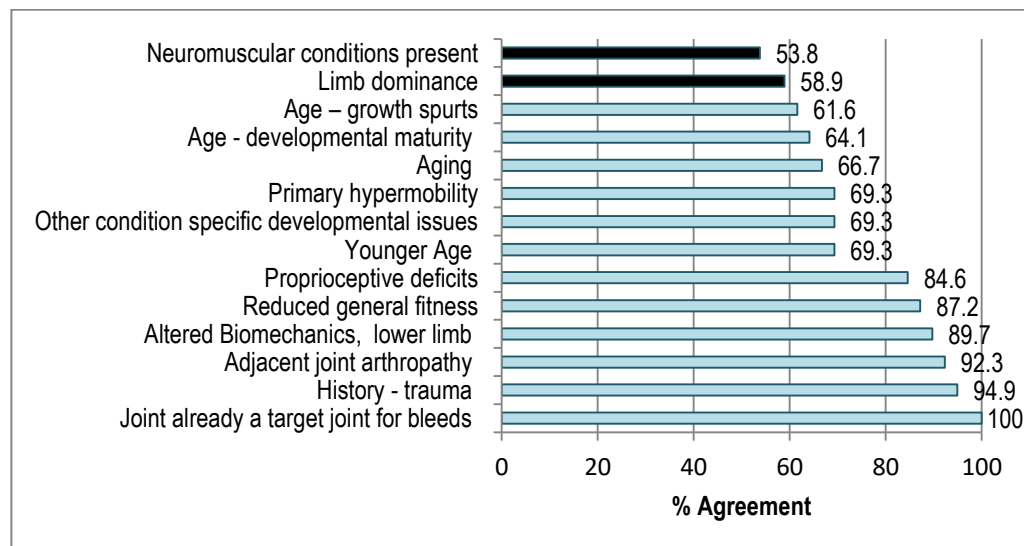


Figure 5.1. Round 2 scoring. Intrinsic factor group. Items in black did not reach consensus.

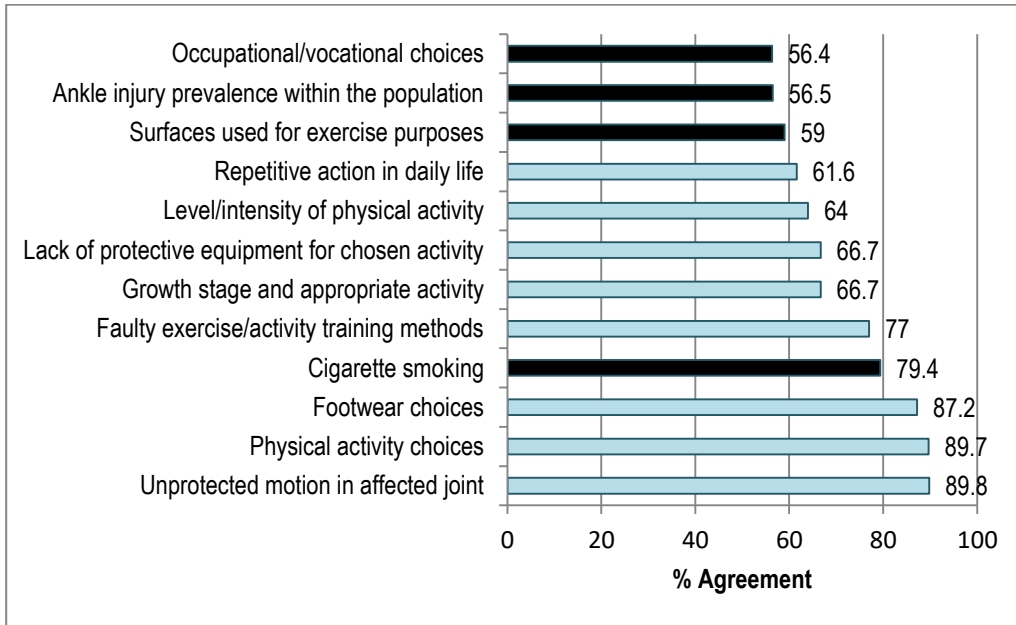


Figure 5. 2. Round 2 scoring. Extrinsic factor group. Items in black did not reach consensus.

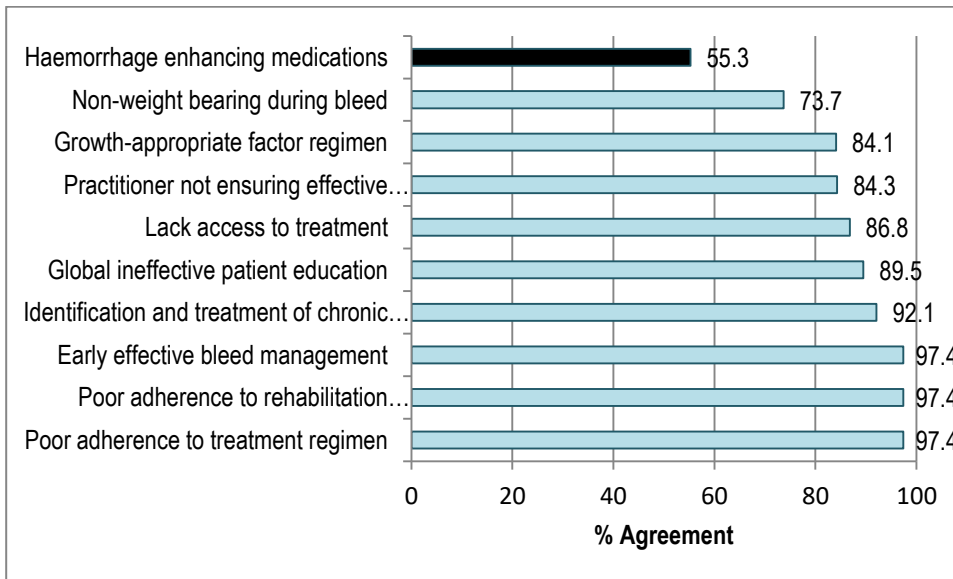


Figure 5.3. Round 2 scoring. Compliance & Education factor group. Items in black did not reach consensus.

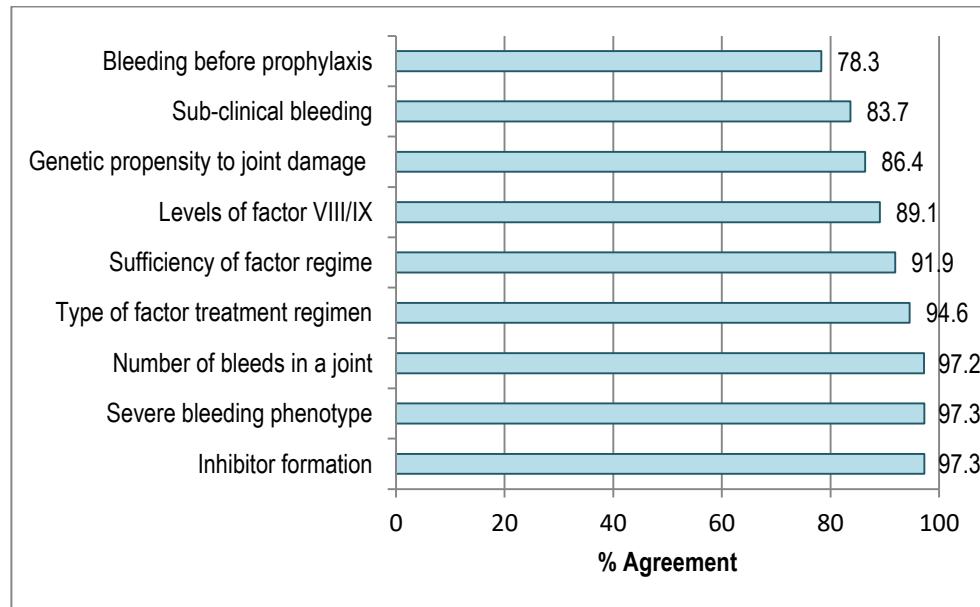


Figure 5.4. Round 2 scoring. Haematology factor group. Items in black did not reach consensus.

5.5.3 Round 3

The participant group for Round 3 was the same as for Round 2 and 31/55 panellists or 56% completed all questions in the round. This represents a 6-panelist drop out between Rounds 2 and 3. Figure 5.5 shows the voting in this round. Of the 14 factors put forwards, 10 reached consensus and 4 were submitted back to the research team for a final decision. This is elaborated upon in the discussion. To summarise the results, 48 factors were rated over two Rounds and 42 reached the pre-specified levels for importance and consensus. Two were considered unimportant and were discarded (consensus for rejection) and 4 were referred to the research team for final decision and were also discarded. These were: “Limb dominance”; “Haemorrhage enhancing medications”; “Activity at a younger age” and “Neuromuscular conditions present”.

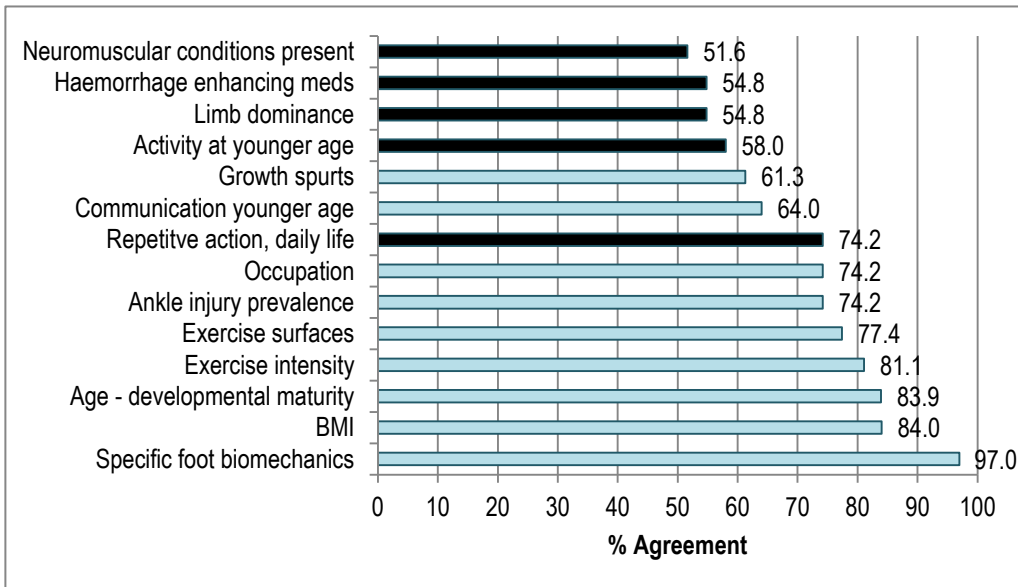


Figure 5.5 Round 3 scoring results. Black bars indicate items not reaching consensus.

In order to use these results to guide the onward research process, the research team met to discuss the feasibility of investigating each factor. The results of these discussions can be found in section 5.7.

5.6 Discussion of the Study

Through the Delphi process the wide range of potential factors that clinicians believe have the potential to influence the development of HA at the ankle, have been explored. This research reinforces the utility of Delphi as a research approach to generate ideas and seek opinion. Forty-eight factors were generated, rated and validated using a three-round Delphi process, with the result that 42 out of 48 factors reached the levels set for importance and consensus.

The heterogeneous panel of clinicians, researchers and academics from a range of specialties, countries and professional backgrounds provided a unique perspective on the subject under discussion. The low drop-out rate across rounds

demonstrated a commitment towards the subject by the panel and the researcher considers that the multi-professional nature of the panel minimised the risk of participant bias (Duffield, 1993). The rationale and comments provided by the panellists acted to strengthen the validity of the findings. As factors were generated by the panel, they possessed high face and content validity (Baker, et al., 2006). The former refers to the extent to which the generated data represent the facets of a given situation and the latter refers to the extent that all facets are represented.

Whilst the make-up of the panel and definition of what it is to be an expert has been described as a weakness of the Delphi process (Sackman, 1974), these criticisms mainly date from its earliest uses for military and financial forecasting. In the current study after reviewing the literature, a broad definition of expert was taken. It was felt that many clinicians would be able to contribute positively to the survey without benefit of a specific number of years in a specialism or gaining of a specific qualification; a position supported in the literature (Duffield, 1993). PWH who volunteered were taken at face value as experts.

As a generality, it has been stated that as the group chosen for Delphi is not a random sample of the target population, their output cannot be representative (Donohoe & Needham, 2009). This might be correct technically however the facilitator has no control over who will accept the invitation so the panel represents a random selection of invitees. It is also claimed that giving the same survey to different groups would result in different outcomes, however both Duffield (1993) and Hardy et al. (2004) analysed results of one survey by multiple groups and found little difference at the point of consensus. This would imply that there is little grounding to the claim that a Delphi panel cannot be representative.

Across the three rounds of the Delphi, 47 panellists from 11 countries consented to take part. The majority of those were from the United Kingdom which could be perceived as bias towards the ideas and opinions of that country. Future panels might be strengthened by ensuring equal numbers from each participating country where feasible and of each type of clinician.

The purpose of the current survey was to generate investigation topics for inclusion in future studies. It has been noted that for certain topic areas there is the possibility that panellists will all provide similar responses and so to counter this it has been recommended that they be asked for at least six opinions to encourage them to explore the issue fully (Schmidt, 1997). This study requested up to ten responses and not all panellists achieved this but all provided six. The researcher considers that this was fundamental to the breadth of factors suggested by the panel which was in excess of the researcher's expectations.

The introduction to the survey emphasised its importance and how results would be used to guide future research. Several of the cited papers used reminders to encourage participation and authors stated that this had had a positive result on participation (e.g. (Hardy, et al., 2004)). The researcher utilised the reminder facility in the survey software in an attempt to facilitate a similar reaction. However there was still a drop off in participation from Round 2 to the Round 3. The researcher deems that this may be a reflection of panel fatigue or the timing of the final round during the summer holiday period.

Agreement and consensus thresholds were assigned to the study following a thorough review of pertinent literature and discussion with a statistician. Selection of a moderately high point of importance for this study was determined by its

purpose and recognised the potential for factors to conflate in their action on an individual. The moderate agreement and consensus levels set also recognised that the panel were international and were likely to have some basic differences in training and values (Rushton & Moore, 2010) and additionally were from a variety of clinical backgrounds with the associated emphases in education.

A method of data analysis has been recommended in the literature by Holey et al. (2007) to ensure maximum validity of the results (Holey et al., 2007), however, the method requires that a classical rating process is carried out which did not occur in this study. Therefore a procedure of percentage agreement was settled upon and in the current study the criteria for a 60% threshold was determined following the study of Duffield et al. (1998).

Holey et al. (2007) also recommended the use of a Likert scale mean score for analysis purposes and Hardy et al. (2004) treated the scale as continuous data. The researcher did not concur with the choices of Hardy et al. as the underlying concept for the use of the Likert scale as an ordinal data form should be considered prior to doing so (Grace-Martin, 2016). In this case it was used to assess panellist's attitude to degree of importance, which the researcher considered highly subjective, and so intervals between points would be difficult to define as equal. Although justification of using the Likert scale as continuous data under certain conditions can be found in the literature (e.g (Glass, Peckham, & Sanders, 1972)), it is also recommended to ensure that the data sets obey the assumptions required for parametric testing such as normal distribution and equality of residuals. A further recommendation was that a more stringent alpha level should be set to ensure that results are strongly significant to ensure that the

manipulation of assumptions has had no clear effect on the outcome (Grace-Martin, 2016). In studies that the researcher has reviewed using a mean score, the above recommendations have not been reported. Moreover, the researcher felt that the purpose of this Delphi, to identify and rate potential factors for investigation, did not warrant statistical analysis to ensure stability of response or increasing consensus across rounds.

A feedback point from Round 2 highlighted that a factor might be considered more or less important dependent on the condition of the PWH at the time of assessment. This is a valid point. With all potential influencing factors, their impact will change on a daily basis recognising that a person is a dynamic system who will alter depending on that moment's circumstances; this ties in with the premise of the thesis.

It had been intended to include PWH and/or their parents/carers in the Delphi study. However, recruitment proved difficult and only three data sets were gained for Round 1. The researcher considers that the poor recruitment occurred for several reasons. The advice to advertise on social media may not have been sound as it was unknown how many people actually regularly visit the webpage. Also, in approaching PWH directly, the value of their experience to the research project may not have been emphasised well enough and potentially a face-to-face facilitated group forum may have produced better data.

In the final rating round, four factors did not reach consensus. Decisions for retention or exclusion of the factors made by the research team were based on the panellist's rationale for their position, a review of available literature, existing empirical clinical knowledge and feasibility within the research programme, and on

this basis all four were discarded. This left the researcher with 42 factors to consider for onward study and a feasibility review was undertaken in order to decide which factors would be included in the main case control study the results of which are discussed in the next section.

5.7 Discussion of the Findings

In order to manage the surfeit of factors suggested and raised to consensus by the panel, it was necessary to perform a feasibility review to determine the next stage of the research. Maintaining an overview of the working theory, considering the skill set of the researcher, and financial and time constraints of the research programme, factors were reviewed for their potential to be investigated within a single study scenario. The decision for each factor is presented with a brief rationale for its retention or for rejection. It is acknowledged that some retained factors were likely to be considered in a superficial way, but after discussion, this was felt still to be a good starting point and could signpost future research directions. The researcher examined each factor and presented her reasoning to the supervisory team who then ratified the decisions. This process is referred to below as a research team (RT) decision.

5.7.1 Intrinsic Musculoskeletal Factors

Adjacent joint arthropathy. Decision: Discard

The effect of this factor is already known and discussed in the literature. Moreover, as the idea was to investigate isolated ankle arthropathy, the presence of disease in an adjacent joint would affect clinical testing.

Age – developmental maturity. Decision: Discard

The correlation between age and likelihood to bleed is established (Valentino,

Hakobyan, et al., 2012), ascertaining whether this is due to neuromuscular developmental maturity would be difficult and potentially a matter of excluding all other potential factors and therefore beyond the scope of this research programme.

Aging. Decision: Discard

This study was aiming to establish factors affecting children, and so the effects of general aging would not meet this aim.

Altered biomechanics, lower limb. Decision: Retain

Alterations to lower limb biomechanics have been detected in haemophilia cohorts but no connection has been established with pathogenesis of HA (e.g. (Bladen, et al., 2007; Lobet, et al., 2010)).

Body Mass Index (BMI). Decision: Retain

BMI has been linked to increased injury risk in the literature (e.g. (Tyler, et al., 2006)). Additionally an increased BMI could indicate a reduced general fitness level and affect injury risk secondary to this.

Communication at a younger age. Decision: Discard

The RT could not establish a method by which this could be measured.

Additionally, the age group for the main study was going to envelope males with developmentally mature feet and gait patterns where communication was not an issue.

Growth spurts. Decision: Retain

During a growth spurt, bone growth outstrips muscular growth, and around the lower limb can result in altered biomechanics, particular development of transient increased pronation. This may alter loading on the ankle joint complex and gait

pattern.

History of trauma. Decision: Retain

There is much evidence in the literature that a history of trauma and in particular ankle sprain predisposes a person to recurrence of the injury (Tyler, et al., 2006). Repetitive ankle sprain has been linked to the development of OA at that joint (Daniels & Thomas, 2008).

Joint already a target for bleeds. Decision: Discard

This factor has been discussed in the haemophilia literature where a link has been established (Valentino, Hakobyan, et al., 2012).

Other condition specific developmental issues (e.g. dyspraxia secondary to inter-cranial haemorrhage). Decision: Retain

The effects of these conditions on control of joints might predispose to HA development. Prevalence of the factor will be noted in the study cohort.

Primary hypermobility. Decision: Retain

Hypermobility has been associated with symptoms such as poor proprioception, reduced strength, easy bruising, fragile tissues, delayed healing and increased injury risk (Grahame, 2003 ; Maillard & Murray, 2003). There is a possibility that the reduced stability at joints caused by lax ligaments could lead to increased shear forces on the articular cartilage. This clinical presentation suggests that it is a candidate for influencing arthropathy development.

Proprioceptive deficits. Decision: Retain

Reduced proprioceptive function might predispose to either an increased injury risk (Hubscher et al., 2010) or accumulative damage from persistent use of body parts

with altered control strategies (Comerford & Mottram, 2001).

Reduced general fitness. Decision: Retain

Fitness encompassing strength and cardiovascular sufficiency amongst other aspects could affect in the first instance a person's ability to control their joint and secondly increase the risk to injury associated with fatigue. Improving strength as a means to reduce bleeding rate has some support in the haemophilia literature (Falk et al., 2000; Tiktinsky et al., 2002).

Specific foot biomechanics. Decision: Retain

Alterations to foot biomechanics have been detected in haemophilia cohorts (e.g. Stephensen et al. (2008)) but no connection has been established to the potential pathogenesis of HA. Altered biomechanics may affect ankle joint loading.

5.7.2 Extrinsic Factors Affecting Physical Health

Ankle injury prevalence. Decision: Discard

Although the prevalence of ankle injury has not been established in haemophilia cohorts and an increased rate of injury would be cause for concern, it would be difficult to establish from historical data.

Faulty exercise/activity training methods. Decision: Retain

Evidence in the literature indicates that poor training or overtraining can lead to injury (e.g. (Gabbett & Domrow, 2007)). An overview of reasons for injury in a PWH cohort would be beneficial.

Footwear choices. Decision: Discard

Although the RT felt there was empirical evidence for this factor, it was felt difficult to include within the time constraints of the planned single study.

Growth – stage appropriate activity. Decision: Retain

The researcher has suggested that there is an age range during which articular cartilage is more vulnerable to attack. Additionally growth spurt changes may affect a person's ability to tolerate exercise load. An overview of activity patterns may help establish any patterns.

Lack of protective equipment for chosen activity. Decision: Retain

Choosing to omit recommended safety equipment for a chosen activity may increase the risk for injury.

Level/intensity of physical activity. Decision: Retain

Along with a lack of understanding of what kinds of activity introduce increased risk to the ankle joint, other factors pertaining to exercise exposure are also unknown, such as what exercise dosage is safe? Also, do people exercising at higher levels sustain more bleeds through exposure or less through increased fitness, know-how and coaching?

Occupational choices. Decision: Retain

There is a possibility that occupations with greater weight bearing components perpetuate arthropathy development although they are unlikely to be capable of initiating the process as this starts much earlier in life.

Physical activity choices. Decision: Retain

The type of physical activity chosen may have an impact on joint loading and risk of

injury. Furthermore deficiencies in the physical requirements to perform the activity well may also increase risk of injury.

Surfaces used for exercise purposes. Decision: Retain

There is some indication in the literature that running on harder surfaces increases risk of overuse injury. Moreover, running or other exercise on uneven or softer surfaces such as sand could lead to increased injury risk.

Unprotected motion in affected joints. Decision: Discard

This factor refers to motion in joints already affected by HA and so is not relevant to determining the potential for the factor to influence HA development.

5.7.3 Compliance, education and non-medical management factors

Early effective bleed management. Decision: Discard

The RT felt that this factor represented multiple aspects all of which would warrant major investigation and so could not be included within the confines of a single study.

Global ineffective patient education. Decision: Discard

Haemophilia centres take great care in trying to educate PWHs and their close relations, having developed age appropriate materials in several formats, however the issues raised might suggest that these may not be having the required impact. As with the previous factor, the scope of this single factor is too great to include within a single study.

Growth-appropriate factor regimen. Decision: Discard

The RT felt that this factor was outside the scope of the researcher.

Identification and treatment of chronic synovitis. Decision: Discard

This factor represents a very large subject area that could not be addressed in a satisfactory way as part of a correlational study. It is also mainly outside the scope of the researcher.

Lack of access to treatment. Decision: Discard

This factor represents a very large subject area also encompassing geography and healthcare provision that could not be addressed in a satisfactory way as part of a correlational study.

Non-weight bearing during a bleed. Decision: Discard

The RT could find no rationale in the literature to support or explain this factor. Additionally, condition management was not within the scope of the research programme.

Poor adherence to rehabilitation. Decision: Retain

Using Lateral Ankle Sprain as an example, there is evidence that following injury many intrinsic factors do not return to normal. For example, reduction in bilateral gluteus medius activity has been noted (Bullock-Saxton, et al., 1994) which could lead to altered lower limb biomechanics. It was felt that a superficial understanding of PWH attitudes to this could be gained.

Poor adherence to treatment regimen. Decision: Discard

Adherence to the medical management regimen was a subject area that may affect arthropathy development but lies outside of the researcher's field.

Practitioner not ensuring effective rehabilitation. Decision: Discard

The RT considered that investigating this would be complex as it is unknown what physiotherapy consists of around the UK and why, and so at the very least some form of benchmarking exercise would be required which is outside the scope of the research question.

5.7.4 Haematology Intrinsic factors

Bleeding before prophylaxis. Decision: Discard

The RT considered that it would be difficult to ascertain this phenomenon in the PWH participants without involving their parents.

Genetic propensity to bleeding. Decision: Discard

Investigation into this area is beyond the scope of the researcher. However the genetic haplotype will be recorded where available.

Inhibitor formation. Decision: Retain

Bleeding is difficult to control in boys with haemophilia who develop inhibitors. The literature does not clearly indicate whether they have a higher propensity for HA development. The history of inhibitor formation will be noted in the PWH population.

Levels of factor VIII/IX. Decision: Retain

The level of circulating factor VIII or IX is a basic indicator of tendency to bleed with those with less than 1% classed as having a severe presentation and the possibility of bleeding with little or no provocation.

Number of bleeds in a joint. Decision: Retain

Although it has been suggested that a minimal amount of exposure of articular

cartilage to blood may be enough to initiate degenerative processes (Roosendaal, Vianen, et al., 1999), the amount or number of bleeds has not been ascertained. Determining the number of bleeds may help elucidate this area.

Severe bleeding phenotype. Decision: Discard

Investigating bleeding phenotypes would be outside the scope of this research programme and the skill set of the researcher. However classification of disease severity will be noted.

Sub-clinical bleeding. Decision: Discard

Determining the presence of sub-clinical bleeding has not been attempted in the haemophilia literature and is beyond the scope of the researcher.

Sufficiency of factor regimen. Decision: Discard

Investigation into this area is beyond the scope of the researcher.

Type of factor regimen. Decision: Retain

Evidence suggests that a prophylactic factor regimen is on the whole effective at limiting joint bleeds (Manco - Johnson, et al., 2007), and so type of regimen will be noted in the PWH cohort.

Therefore following a feasibility review 22 factors have been selected for onward evaluation of which 17 will be actively investigated and the presence of remaining five will be recorded. In practice the consequences of the factors from each category and how they act on the person have to be seen in the framework of the variability between individuals, and within individuals over time.

5.8 Conclusion

Using the flexibility inherent in the Delphi process, each round was modified to

respond to the incoming data and to ensure the research aim was satisfied. A wide range of research suggestions was generated resulting in 42 factors reaching the benchmarks for importance and consensus. These results have also been published in a peer review journal, see Appendix 1. Hardy et al. (2004) remind us that the meaning of an item reaching consensus and high importance is not a direct measure of the true value of the item itself, but rather the opinion of the panel, and that this item must undergo further investigation to assess its actual relevance to the subject under investigation. Therefore, the selected factors have guided the development of second phase of the research programme, a case-control correlational study investigating the potential of the said factors to influence the development of HA. The following four chapters present the evolution of this study. Chapter 6 will present the study design and describe its protocol. In Chapter 7, the selection of the assessment battery is described in detail, and Chapters 8 and 9 present preliminary development work.

Chapter 6 Main Study: Evaluation of the Effect of MSK and Exercise Factors on the Development of Joint Disease in Haemophilia - Study Design, Methods & Implementation.

6.1 Introduction

An international, multi-professional panel undertaking a Delphi process, fully described in Chapter 5, were of the opinion that the pathogenesis of haemophilic arthropathy (HA) is multifactorial and that factors could be derived from a multitude of sources both intrinsic and extrinsic to the person. A feasibility review of the 42 factors that had reached pre-set levels for importance and consensus concluded that 22 could be investigated to varying degrees within a single mixed methods study design. Considering the researcher's conceptual framework, that the development of HA follows a recursive, non-linear pathway, the researcher considered that only by investigating as many of the potential factors concurrently and analysing them together, could a more complete picture of their influence on HA development be advanced. With so many variables in play, the actual study design required careful consideration so as to ensure results were produced with real world applicability. This chapter and the three following, describe the maturation of the study from its design into a fully ready protocol. In this chapter the choice of research design is explained together with a rationale as to how it could meet the objectives of the study. An overview of the study protocol including the rationale for group selections is presented. It considers site preparation, logistics and later in the chapter, reliability and an overview of the data management process. The selection and detailed descriptions of the assessment tools are presented in the following three chapters.

6.2 Study Objectives

The **primary objective** of the study aimed to address the overall thesis purpose, to wit, to explore the ways that non-haematological factors contribute to the development of ankle haemophilic arthropathy and how these factors could be identified.

This led to the formation of the following specific **secondary objectives** for the study:

- To evaluate the influence of intrinsic musculoskeletal and extrinsic exercise factors on the development of ankle arthropathy in people with haemophilia in order to identify people with a high risk of arthropathy phenotype.
- To understand the relative contribution of intrinsic musculoskeletal factors to the development of HA in those that are at a high risk of developing the condition to enable personalised interventions.
- To explore the influence of extrinsic factors affecting physical health that can influence the development of haemophilic arthropathy.
- To evaluate the efficacy of the test protocol with regards to:
 - identifying the presence of HA
 - rationalising the protocol and developing a model for data analysis.

6.3 End Points

- Univariate analysis will be carried out on measures of strength, balance, co-ordination, flexibility and fitness (aspects of musculoskeletal health) to identify

factors with significant correlations between the variable and haemophilic arthropathy

- Variables reaching significance will be entered into multivariate regression analyses in order to assess their relative influence on haemophilic arthropathy development.
- Parameters of exercise choices will be considered as co-variables in the analyses.

6.4 Study Design

The full protocol for this study is attached as eAppendix 9, and it should be noted that, as explained in Chapter 1, aspects not encompassed in this doctoral study are included. For practical purposes, the full research programme is occurring in stages; this thesis presents the first stage. The first stage includes an initial data collection period followed by an initial data analysis in order to ensure the efficacy of the chosen study protocol.

A research design whereby potential factors were correlated with the presence of HA was necessary. This resulted in the selection of a case control correlational study design. Case-control studies are differentiated from cohort studies by two features:

1. sampling by disease as opposed to sampling by exposure
2. investigation moves from effect to cause rather than from cause to effect.

A correlational study is one in which the presence of variables are compared to see if any relationship exists between them. There is no dependent and independent variable per se and so this type of study cannot determine cause and effect (Hicks,

2009b) however, regression analysis can be used to determine the relative influence of any significant findings determined by univariate analysis. The groups in the case-control study should control for attributes contained within the key group of interest so that differences between groups can be attributed to measured variables and not to the presence of the disease in question. To follow this principle the key group for this study was identified as: people with haemophilia (PWH) with ankle joint HA. Therefore, there was a need to control for the haemophilia and the ankle joint disease and so ideally three other groups would be required: PWH-no joint disease, no haemophilia-ankle joint disease and normal volunteers.

In order to evaluate the efficacy of the test protocol (a secondary objective) and ensure that the study was progressing well, the first stage data collection encompassed three groups. The fourth group, ankle joint disease with no haemophilia, will be recruited to in the second stage post-doctorally. So to reiterate, the study groups for the first stage of the case-control study were:

- People with haemophilia and dominant ankle joint arthropathy (HmAk)
- People with haemophilia with no clinical joint arthropathy (HmC)
- Normal volunteers (NV)

Membership of these groups is described in the next section.

6.4.1 Research Governance

Following the development and ratification of the case-control study test protocol by the supervisory team, the study was submitted for ethical and research governance approval from the University of Brighton Ethics and Research Governance Committee (FREGC 14-034, Appendix 4) and the National Research Ethics Office East of England Committee (14/EE/1137, Appendix 4). Ethical

approval was gained on 24th September 2014. The study was funded by an Investigator-Initiated Research grant from Pfizer Ltd (see eAppendix 10). Immediately following this, local Research and Development approval was sought at all participating trusts. NIHR portfolio adoption occurred on 28th October 2014. The Chief Investigator (CI), supervisory team and local Research & Development personnel were responsible for overall research governance. At each site the Principal Investigator (PI) was responsible for the conduct of the study locally.

6.5 Recruitment and Screening

6.5.1 Recruitment & Consent

6.5.1.1 Centre Recruitment

The population prevalence of haemophilia A and B and inclusion criteria detailed below meant that it was not possible to recruit the required study numbers at a single centre. Therefore it was necessary to approach other treatment centres and this was achieved via the haemophilia centres clinical network whereby centre directors were contacted by the host centre consultant haematologist to ascertain their willingness for participation. The physiotherapist in each centre was contacted informally and directly by the researcher to explain the study in detail and the commitments required to participate. The co-ordinating centre for the study was the Katharine Dormandy Haemophilia and Thrombosis Centre (KDHC) at the Royal Free London NHS Foundation Trust. Additionally four NHS treatment centres agreed to take part in the recruitment of the haemophilia groups. These were: St Thomas's Hospital London, Manchester Royal Infirmary, Basingstoke Hospital and Oxford Churchill Hospital. At each site the PI was the centre physiotherapist,

except at the host centre where the PI was a consultant haematologist as the researcher was designated CI.

6.5.1.2 Participant Recruitment

Participants were recruited by the direct health care teams using their clinical databases and the personal knowledge of the PI at each site of their clients. The researcher reviewed client databases with the PIs so that all were approaching selection in the same manner. PI knowledge of local participant response to previous requests for research participation determined whether the actual approach was in person during clinic visits or via postal invitation. Some centres combined both approaches. All approaches abided by the principles of NHS research governance. Healthy controls were recruited at the co-ordinating centre via email, poster and notice board advertising, and word of mouth.

The background to the study, the procedures, benefits and risks of the study were explained to the potential participant by the PI. It was made clear that taking part was voluntary and that the participant could choose to withdraw at any time. Good research practice required that participants were given a minimum of 24 hours to consider their participation. Multiple information sheets were developed to account for the differing reasons that a person had been asked to participate. For those under eighteen years, age appropriate information was provided. The minimum age for participants was 12 years of age which required information measured at grade level 8 on the Flesch-Kincaid Grade level reading ease score or a Flesch Reading Ease level of around 60% - 70% (Scott, 2012). The paediatric information sheet provided in this study measured at grade 7.4 and 72%. Participants and/or parents/guardians where applicable, provided consent before any participation.

See appendices 5 and 6 for example Participant Information and Consent Sheets with the rest appended electronically e9-22.

6.5.2 Rationale for Inclusion Criteria

Reasoning behind specific group criteria and other issues are discussed in more detail below. The full inclusion and exclusion criteria are presented in Table 6.1.

Group 1: People with haemophilia and dominant ankle joint arthropathy (HmAk)

Inclusion criteria needed to be determined for the key group that would result in a group with demonstrable ankle arthropathy but with reasonably normal function.

The study was looking to establish factors that could influence initiation or perpetuation of ankle arthropathy, and so the participants needed to be early enough in the disease process so that the arthropathy itself would be less likely to directly affect test results. That is, marked functional limitation in any lower limb joint would result in some tests showing a very pronounced tendency towards

Table 6-1 Inclusion and Exclusion Criteria

<i>Inclusion criteria</i>		
All Groups		
Participant is willing and able to give informed consent for participation in the study		
Male, aged 12 to 50 years.		
Haemophilia ankle joint disease	Haemophilia no joint disease	Normal volunteers
Haemophilia A or B with predominant ankle joint problems: bleeding into the ankle joint, pre-clinical, or mild signs of arthropathy able to perform a step-up to a 24cm step and with a functional gait.	Haemophilia A or B with healthy limb joints. 50% of the patients will have a factor VIII or IX level of >10%.	No lower limb joint disease or history of major trauma to the lower limb joints.
Knee arthropathy may be present at grade 1, must be less symptomatic than the ankle. Presenting without functional limits.		
<i>Exclusion Criteria.</i>		
The participant may not enter the study if ANY of the following apply		
All Groups		
Inability to perform step up to a 24cm step & ankle motion below that necessary for normal gait.		
A history of unstable hypertension or cardiac disease or use of beta blockers.		
Any lower limb injury in the last 6 months.		
Any ear or eye condition or injury, or any history of head injury that could affect balance.		
Unable to provide informed consent/assent or complete surveys in English		
Haemophilia ankle joint disease	Haemophilia no joint disease	Normal volunteers
Person with an actively bleeding joint may not be seen on the day.		
Presence of knee arthropathy with marked functional limitations.		
Open surgery to the ankle or knee joints.		

dysfunction due to the degree of joint degeneration. This would make it impossible to determine whether the results were related to the aetiology or were effects of joint disease.

One initial proposal to select those with early joint disease was to use the Haemophilia Joint Health Score (HJHS) (Hilliard, et al., 2006) which is a standardised score that has become internationally utilised despite some recognised weaknesses (i.e. lack of full validation in adults). A cut-off score of greater than 6 on any given joint has been suggested to identify a problematic joint (Feldman, 2011). However, depending in which domains the scoring occurs, it is possible to reach that score and yet maintain a highly functional joint. MRI of the joint would provide a gold-standard of joint status however this was not feasible financially or logistically. Therefore both the HJHS and MRI were rejected as selection criteria and functional criteria were identified that are recognised as key within the literature such as the amount of dorsiflexion required for a normal walking gait pattern. Additionally, as the selected aerobic test included a stepping up motion, the ability to step up a 24cm step was required. This allowed a flexible approach to recruiting into this group in order to maximise the potential pool of candidates.

Group 2: People with haemophilia with no clinical joint arthropathy (HmC).

As all haemophilia participants were recruited based on their clinical and functional presentation, the HJHS provided an easy way of identifying those without joint problems from records. Therefore although it was not viable for use in selecting the HmAk group, a zero score was used to identify those with no apparent joint disease along with the aforementioned functional criteria. The researcher actively attempted to recruit across a range of residual clotting factor levels in order to represent all severities of haemophilia and ascertain population prevalence for specific experimental variables.

Group 3: Normal volunteers (NV)

Owing to the researcher's professional background as a physiotherapist, there was a potential to bias this group by recruiting heavily from professional colleagues as the group is generally considered to be fit and active. In order to counter this, staff from the haemophilia centre who hold sedentary working positions were also recruited and people from outside the trust with a wider variety of professions. The younger people recruited were children of staff or friends.

General inclusion considerations

Overall an age range of 12 to 50 was selected to recognise both gait and proprioception maturation, and then decline. 12 years of age is adequate for maturation of the foot into adult posture and of the ankle/foot for adult gait pattern, proprioceptive ability and passing of transient childhood hypermobility (Donatelli, 1990; Skeith et al., 2010). After 50 years of age, balance ability is known to reduce (Balogun et al., 1994) and this would skew results.

6.5.3 Exclusion Criteria

6.5.3.1 General considerations

These are divided into absolute and on-the-day exclusions. Absolute exclusions reflected other medical conditions with the potential to influence any aspect of the testing such as cardiac disease requiring beta blockers which had the potential to influence fitness testing. Other absolute exclusions reflected the potential to influence balance or proprioceptive mechanisms. Proprioceptive mechanisms include mechanoreceptors local to joints but also visual and vestibular mechanisms.

Open surgery to the lower limb joints was deemed an exclusion criterion for the HmAk group as the presence of an incision might impair proprioception due to cutaneous nerve severing and there may also be scar tissue present affecting joint mobility. Additionally, as there was a fitness test involved, it was necessary to ensure that the participant was fit enough to take part on the day of testing. Therefore, the participant had to present with a resting heart rate of under 100 beats per minute and a systolic blood pressure under 150mmHg on the day of testing (Reilly & Tipton, 2010).

6.5.3.2 Haemophilia Ankle group

The presence of a bleed on the day of testing or in the 6 weeks prior to attendance would prohibit testing for a number of reasons from pain to bleed-related muscle inhibition. However, once the bleed had resolved and the participant returned to their baseline, they could take part.

6.6 Site preparation

The researcher was CI and at all other sites the PI was an incumbent chartered physiotherapist. None had undertaken this role before but all had acted as investigators for various haemophilia-related studies. Therefore the CI explained their responsibilities in this role and provided a site file with all relevant documentation at the site initiation visit which lasted on average 3 hours.

6.6.1 Investigator preparation and reliability considerations

With a number of sites and investigators in operation, inter-rater reliability is a consideration. The researcher sought to ameliorate the potential issues as far as possible. Logistically bringing all investigators together was not feasible in advance

of study initiation due to the staggered “Research & Development” approvals and hence onsets of data collection. Additionally some investigators were part-time and so time commitment was difficult. Therefore methods selected to address inter-rater agreement were:

- Provision of a detailed instruction manual for the clinical and survey measures for each PI.
- One-to-one or small group training with the researcher in order to ensure techniques matched the instruction manual prior to opening the site. Please see the text below for detail.
- Provision of matching equipment for each clinical test to reduce the likelihood of measurement error.

The protocol for each measured test was selected so as to minimise the opportunity to introduce bias and measuring was, as far as possible, performed electronically to minimise operator error and operator bias.

The CI undertook training with each site’s investigator/s in order to ensure that procedures were carried out in as similar manner as possible. The CI’s technique and opinion of the test result were used as the gold standard. Training sessions were at least three hours. Clinical tests were performed on volunteers who fed back to investigators on whether hand placement and pressure felt the same as when the researcher performed the test. The PIs and researcher then compared results to ascertain whether agreement had been reached. Where possible, and volunteers were available, this occurred multiple times. The tests with greatest subjectivity were the Foot Posture Index and the Ankle Anterior Drawer Test (both tests will be described in Chapter 7) and so PIs were requested to practice these.

Local PIs were free to video or photograph the sessions to aid their learning. The assessment protocol was enshrined in a Standard Operating Procedures (SOP) document (eAppendix 23). The SOP specified the exact procedure for each test and described the necessary set-up for the assessment. The CI/researcher also kept in close contact with the investigators by phone, email and also carried out site visits to ensure continuity of data collection techniques. Each questionnaire was also discussed.

The researcher considered it unfeasible to perform intra-rater reliability on the full assessment protocol as the participants were being asked to commit to approximately a ninety minute testing protocol in the first instance and usual attendance for review for the haemophilia cohorts is six-to twelve-monthly. It was felt that the study would struggle to recruit even a reduced sample on the basis of multiple visits.

6.7 Assessment Tools

The complex task of selection of assessment tools is discussed in detail in Chapters 7, 8 and 9. Table 6.2 presents a list of the chosen tools here in order to sustain the flow of the narrative in this Chapter. A brief rationale for their inclusion and where each test can be found in the upcoming chapters is given. Please note the description of their application can be found in the SOP, e-Appendix 23.

6.8 Pre-Testing of Assessment

Once the assessment battery had been assembled it was necessary to trial it in terms of duration and participant acceptability. The assessment was performed with two haemophilia specialist physiotherapists who confirmed that they believed

it was physically appropriate to the PWH under study. They also helped determine the exact method of performing the tests which was recorded in the SOP manual.

The assessment was then performed with a self-declared unfit lay person. This determined that the examination would take a maximum of one hour and 45 minutes if the participant performed to the maximum limit of the timed tests. After this, a PWH undertook the assessment and deemed it acceptable in terms of joint load, effort and time. Therefore the researcher considered the test protocol appropriate to proceed with the study.

Table 6-2 Assessment Techniques Included in the Protocol in Order of Application

Tool	Rationale	Chapter placement
Physical Activity Questionnaire	Explores activity, occupation and rehabilitation factors	7.2 & 8
Height & weight	To calculate body mass index (BMI)	7.3
Anterior drawer test	Assesses for the integrity of ankle lateral ligaments and thereby joint stability	7.4
Subtalar range of motion	Assesses joint range of motion	7.5
Great toe extension	Assesses joint range of motion	7.6
Ankle lunge test	Assesses joint range of motion	7.7
Star excursion balance test (SEBT)	Assesses dynamic balance, lower limb co-ordination, quads strength and ankle DF range	7.8 & 9
Foot posture index (FPI)	Gives an evaluation of static foot posture	7.9
Timed single leg stance	Measures static balance ability	7.10
Hypermobility & dyspraxia questionnaires	Give an indication of general hypermobility and associated symptoms	7.11
Single leg squat test	Gives an evaluation of neuromuscular control of the pelvis	7.12
Calf strength test	Gives a measure of calf muscle strength	7.13
Human Activities Profile (HAP)	A survey giving a subjective indication of overall cardiovascular fitness	7.14
Grip test	Gives an indirect measure of quadriceps muscle strength	7.15
Tecumseh step test	A measure of submaximal cardiovascular fitness	7.16
Foot and ankle ability measure (FAAM)	A survey giving a subjective indication of foot and ankle function	7.17
Cumberland ankle instability tool (CAIT)	A survey giving a subjective indication of ankle stability	7.18

6.9 Study procedures

6.9.1 Assessment

Where possible, the assessment session was organised to coincide with a participant's scheduled clinic visit to minimise inconvenience. Investigators ensured that those participants who were on a prophylactic regimen had administered some treatment on the day of assessment. If they had not, the treatment was

administered prior to participation. The complete assessment was carried out in one session. The assessment was organised such that tests requiring the most coordination were carried out early in the session to avoid effects of fatigue and those with a strong strength component were scheduled at the end (see Table 6.2 above for the protocol order). Questionnaires were placed at intervals to allow the participants an opportunity to rest. The first questionnaire, the exploratory activity questionnaire was carried out first as it required 10 – 15 minutes and so gave the participant a chance to relax prior to the safety blood pressure and heart rate check. Participants were regularly asked if they felt ok or if they would like to rest. An example of the completed set of case record form and questionnaires is attached as Appendices 7 - 12.

6.9.2 Medical records

Background information from the haemophilia groups was collected to respond to the selected haemophilia-related Delphi factors and to enhance the clinical picture. The information gathered is provided in Table 6.3. It was acknowledged that not all the information would be available for each participant for instance if the person had come from overseas or if genetic mutational analysis had not been performed.

Table 6-3 Haemophilia Category Delphi Factors and Additional Related Information Derived from Medical Records. Delphi Factors are in Bold Print.

Haemophilia type A or B	History of other arthropathy
Age at diagnosis	History of developmental issues
Age treatment started	Treatment protocol - regimen type
Age prophylaxis started	Halotype/mutational genetic analysis
Number of ankle bleeds in last 1 Year	Clinical phenotypes
Baseline factor level	Inhibitor to replacement therapy now or ever

6.10 Data management & analysis overview

As the intention of the study was to understand the potential contribution of the various factors to the development of ankle arthropathy, it was necessary to first identify which factors appeared to have an impact and then determine their relative contribution to the presence of arthropathy. An overview of the data analysis procedure is shown in flow chart format in Figure 6.1. Usually, when undertaking a study with the intention to utilise regression, the variables that will be assessed have been identified previously from the literature and so a sample size may be calculated a priori. However in this case, the research programme pathway had been to utilise a Delphi process to guide the choice of factors for investigation. Subsequently, case control study univariate analysis was used to identify factors for entry into the regression process making an a priori sample size calculation untenable in this pathway. Instead the number of factors that might be entered into a regression process was calculated based on the cohort study sample size which itself was based on pragmatic principles of condition prevalence and time. Statistical analysis is detailed in Chapter 10 and a glossary of statistical tests used can be found at Appendix 13.

6.11 Conclusions

This chapter has presented the overall case control study protocol and considered the logistical challenges. It is now necessary to discuss the selection of the assessment tools that went into the final assessment battery. Many assessment tools are already available in the published literature and an evaluation of their ability to meet the needs of the participants of the case control study was undertaken. The selection of the assessment tools is presented in the following chapter.

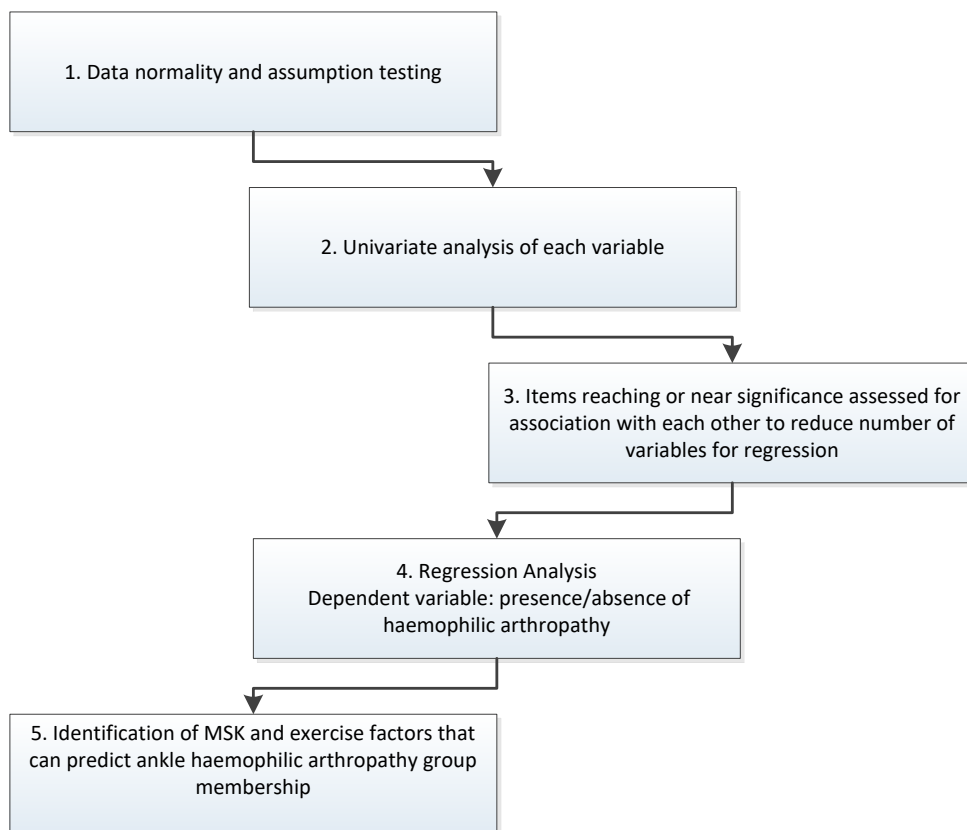


Figure 6-1 Overview of Data Analysis Plan

Chapter 7 Main Study: Evaluation of the Effect of MSK and Exercise Factors on the Development of Joint Disease in Haemophilia - Selection of Assessment Tools

7.1 Introduction

Assessment and survey tools addressing joint health or function exist in the haemophilia pantheon however, they were not validated for non-haemophiliacs and more importantly did not address the chosen Delphi factors. Few studies have been published in the haemophilia literature using non-haemophilia-specific tools (survey or clinical assessment). Fearn et al. (2010) used a battery of clinical and laboratory balance tests on a haemophilia cohort and suggested a set to use to identify deficits in similar cohorts. This study also used a fitness survey called the Human Activities Profile to assess aerobic capacity. Other gait and fitness testing has been carried out largely using expensive laboratory equipment such as video analysis equipment and force-plates (e.g. (Lobet, et al., 2010; Stephensen, 2008)). Therefore the researcher sourced testing procedures from published musculoskeletal (MSK), orthopaedic and sports medicine literature and took expert advice where necessary. The Real-World focus of the research programme meant that it was important that study findings had clinically utility and so only tools that could be used in clinical practice with minimal equipment and low cost were chosen. The researcher also looked for tools capable of multi-tasking by addressing more than one factor during the procedure. Table 7.1 details the all factors investigated and the method/s chosen.

Table 7-1 Delphi Factors Selected for Investigation in the Case Control Study & Selected Measure

Factor	Measure
Musculoskeletal Intrinsic	
Age - developmental maturity	Physical Activity Questionnaire
Age – growth spurts	Physical Activity Questionnaire
Altered Biomechanics of lower limb affecting the foot/ankle	Star Excursion Balance Test, Single Leg Squat Test, Foot & Ankle Ability Measure
History of injury	Physical Activity Questionnaire, Cumberland Ankle Instability Tool
Primary hypermobility	Brighton Criteria, 5-Point Hypermobility Questionnaire, FDQ-9 (dyspraxia questionnaire)
Proprioceptive deficits	Star Excursion Balance Test, Timed Single Leg Stance, Foot & Ankle Ability Measure, Cumberland Ankle Instability Tool
Reduced general fitness	Grip test, Calf raise test, Star Excursion Balance Test, Tecumseh Step Test, Foot & Ankle Ability Measure, Human Activity Profile
Specific foot & ankle biomechanics and anatomy	Ankle dorsiflexion, Great toe extension, Foot Posture Index, Subtalar inversion/eversion, Ankle Anterior Drawer, Foot & Ankle Ability Measure, Ankle Lunge Test, Cumberland Ankle Instability Tool
Weight/BMI	Body Mass Index
Extrinsic Factors Affecting Physical Health	
Surfaces used for exercise purposes	Physical Activity Questionnaire
Faulty exercise/activity training methods	Physical Activity Questionnaire
Growth stage and appropriate activity	Physical Activity Questionnaire
Lack of protective equipment for chosen activity	Physical Activity Questionnaire
Level/intensity of physical activity	Physical Activity Questionnaire
Occupational choices	Physical Activity Questionnaire
Physical activity choices	Physical Activity Questionnaire
Compliance, Education & Non-Haematology Management	
Poor adherence to rehabilitation programmes	Physical Activity Questionnaire

It should be acknowledged that, whilst rooting the assessment protocol in clinical practice was a study attribute the researcher considered essential, in order to enhance the potential for practical applicability, a degree of testing accuracy was sacrificed. For instance, it is likely that static balance recorded via a force plate

mechanism is likely to be more sensitive than that measured with the timed single leg stance test.

In this chapter, each chosen clinical test and survey is presented and discussed in terms of its purpose, rationale both for selection and in terms of the Delphi factor it was addressing, interpretation and any limitations. The exact application for of each test can be found in the SOP manual, eAppendix 28.

7.2 Historical Activity Questionnaire

Purpose. To explore a number of exercise, activity, occupation and rehabilitation factors derived from the Delphi process.

Rationale. The Delphi process raised a number of factors which required examination in an exploratory manner. A questionnaire was considered the best of approach and a novel tool was developed for this purpose. A full description of the development of this questionnaire can be found in Chapter 8.

Interpretation. The data from this survey were divided into that for immediate use in the statistical analysis of the case-control study and that intended to guide and develop future research. Data were mainly presented in descriptive terms.

Limitations. The limitations of this questionnaire are fully described in Chapter 8.

7.3 Body Mass Index (BMI)

Purpose. This measure gives an indication of the percentage body fat of an individual.

Rationale. A higher BMI has been suggested as a predictor for recurrent ankle sprains (Tyler, et al., 2006). Additionally, a higher BMI may indicate reduced overall conditioning in terms of fitness.

Interpretation. BMI is calculated from the formula: $\text{weight} / (\text{height})^2$. BMI is usually compared to normative data indicating a person's position on the continuum from underweight to morbidly obese (nomenclature dependent on graph used). The interpretation differs for children and is dependent on age and sex. However for the purposes of this study group means were compared.

Limitations. Care must be taken with interpretation, as for instance, certain groups may have a higher BMI that does not represent increased fat such as athletes. Additionally, the diagnostic accuracy has been challenged particularly for intermediate BMI levels despite high correlation with percentage body fat measured by bioelectrical impedance (Romero-Corral et al., 2008). Notwithstanding this, BMI remains a well-used and recommended indicator (Hall & Cole, 2006).

7.4 Anterior Drawer Test.

Purpose. To assess the stability of the talocrural joint, in particular the anterior talofibular ligament.

Rationale. PWH and ankle arthropathy may present with a history of recurrent sprains. Empirically they describe feelings of instability. Mechanical instability due to ligament laxity has been cited as a sub-group of those presenting with chronic ankle instability-type symptoms (Hiller, Kilbreath, et al., 2011; Hubbard, 2008).

Interpretation. The motion was graded as 0 = hypomobile; 1 = normal; 2 = moderately lax but within normal limits (end-feel present); and 3 = severely lax.

Limitations. Whilst the diagnostic accuracy of the test is debatable it remains in regular use and may be of benefit in within-person testing and in conjunction with other diagnostic criteria (Croy et al., 2013). In the current context, where unilateral

symptoms are being considered, its use was expedient in that it is well known and simple to perform.

7.5 Great Toe Extension Range

Purpose. To assess the range of extension at the great toe.

Rationale. Great toe extension has been linked with gait abnormalities and predisposition for developing certain injuries. A significantly higher great toe extension range has been reported in a prospective study of people who sustained ankle sprains (Willems, et al., 2005). The method of measurement was not reported. If similar predisposing mechanisms are associated with adversely loading the ankle joint complex (AJC) in haemophilia, then this may also be a relevant indicator. Additionally, more than average range at this joint may indicate small joint hypermobility at the foot. Non-weight bearing goniometry was chosen as the only feasible option. Whilst functional positions may appear more apposite, new methods would need to be devised to control for proximal kinetic chain positioning that might affect the measure, for instance, degree of tibial rotation. Moreover, reliability and validity testing would need to occur.

Interpretation. The range of movement was recorded in degrees. 65° has been suggested as normal range of motion (Munuera, Trujillo, & Güiza, 2012).

Limitations. Whilst the accuracy of goniometric measurement has been debated at various joints around the body with differing reports of inter- and intra-rater reliability (e.g. (Elveru, Rothstein, & Lamb, 1988) and (Hayes et al., 2001)), measures at the great toe have been reported as reliable (Hopson, McPoil, & Cornwall, 1995) and so the researcher considered it the most suitable method available, and attempted to ameliorate error by standardising test performance.

7.6 Subtalar Inversion and Eversion Range

Purpose. To assess the non-weight bearing range of subtalar inversion and eversion range.

Rationale. Subtalar joint motion has been linked with gait abnormalities and predisposition for developing several injuries. It has been shown that there is a great amount of inter-individual variation in the available motion at this joint (Kirby, 1987). Moreover, it has been shown that around 68% of eversion motion is used in the stance phase of gait and that some individuals operate at the outer ranges of this motion potentially predisposing them to injury (Dowdy Youberg, et al., 2005). The researcher considers that it is not unreasonable to suppose a restriction in this motion might increase risk of injury. With respect to inversion, this has often been associated with increased risk of ankle sprain (Delahunt, Monaghan, & Caulfield, 2006; Monaghan, Delahunt, & Caulfield, 2006) although the evidence appears not wholly conclusive. In the face of limitation at the subtalar joint, it is not inconceivable to suppose transference of loading to adjacent areas (i.e. talocrural joint and more distal foot joints). A standardised goniometric measure has been chosen.

Interpretation. The range of movement was recorded in degrees.

Limitations. The limitations of goniometry have been discussed in 7.5 above. Whilst it has been shown that manual measurement of the subtalar joint does not achieve the ranges occurring in fully weight bearing positions (Dowdy Youberg, et al., 2005), the researcher has chosen testing methods with high clinical utility acknowledging that 3-D motion analysis systems and other equipment is not available to most clinicians.

7.7 Ankle Lunge Test (ALT).

Purpose. To carry out a weight-bearing active measure of ankle joint complex dorsiflexion.

Rationale. Ankle dorsiflexion range has been shown to be affected by sprains (Vicenzino et al., 2006) which may lead to compensatory increased pronation. Over a prolonged period this could result in adverse alterations in contact pressures within the talocrural joint and potentially incitation of arthropathy. Goniometric measures of dorsiflexion have been found to be highly unreliable (Gatt & Chockalingan, 2011). The ALT is functional and has been shown to be reliable with excellent inter-rater and intra-rater reliability of above 0.97, with a smallest detectable difference of 13.8mm in a post-fracture cohort

Interpretation. The distance from the wall to the foot (or knee) was recorded. Where the participant was able to move the foot away from the wall and maintain the heel on the ground, a positive measure was recorded. If the participant was unable to touch the wall a negative measure was recorded. The greater the positive measure, the greater the range of AJC dorsiflexion.

Limitations. Gatt and Chockalingum (2011) in their systematic review of dorsiflexion measures noted that a lack of control of pronation during the test may result in false negatives as dorsiflexion can be created through the midtarsal joints and so a relative ankle equinus could be masked. An approximate subtalar neutral position may alleviate this but as determining this position is debatable in the literature (e.g. (Kirby, 1987)) and may actually add to the error potential. So, the researcher concurred with the Gatt and Chockalingum's ultimate recommendation of not controlling the rearfoot.

7.8 Star Excursion Balance Test (SEBT)

Purpose. This test assesses intra and inter subject variability in lower limb dynamic balance, strength and co-ordination.

Rationale. Given the age range and high levels of function in the study populations, balance tests were excluded if they been developed for the specific task of assessing balance in an older population at risk of falls (e.g. The Timed Up & Go Test (Podsiadlo & Richardson, 1991)). Also, given the aim to minimise the length of the testing protocol and combine factors under test where possible. A test of dynamic balance would address, at least in a global manner, control of the lower limb, some dynamic range of motion at the ankle joint and challenge strength in specific ways (Earl & Hertel, 2001; Olmsted, et al., 2002). The SEBT has been found to be a valid and reliable test, however the original test protocol and shortened protocols most recently used in the published literature may not represent the most efficacious protocol to address the factors under consideration in the current study cohort. Therefore, the researcher deemed it necessary to perform a preliminary study into the activation of the gluteal muscles during the SEBT in order to select the best protocol. A full description of this study and its results can be found in Chapter 9. This section will however go on to describe the SEBT application used in the case control study.

Interpretation. Both individual reach directions and a composite score have been used in the literature. The researcher chose to analyse individual reach directions in order to recognise the specific physical challenges that they represented. Moreover, both mean and maximum reach distances have been used in the literature. The researcher recorded and used both in analysis to investigate if there was a strong association between methods.

Limitations. The SEBT, even with a shortened protocol, can be a time consuming procedure. However, the researcher considers that its ability to test multiple aspects of physical performance outweigh the time taken.

7.9 Foot Posture Index (FPI)

Purpose. This test allows a speedy assessment of foot type in clinic without the necessity of measuring tools.

Rationale. An indication of static foot posture is a good starting point for assessment of lower limb biomechanics (Redmond, Crosbie, & Ouvrier, 2006). An obvious loss of the medial longitudinal arch in stance may indicate hypermobility within the foot that is not accounted for in other validated general hypermobility scores. It has also been noted to correlate clinically with the presence of lower limb of conditions such as knee osteoarthritis and patellofemoral pain syndrome (Barton et al., 2011; Reilly et al., 2009). There is growing evidence of the FPI's ability to predict aspects of dynamic foot behaviour such as motion of the centre of pressure and rear foot function (Chuter, 2010; Wong et al., 2008). A stand-alone measure of arch height may also suffice but requires accurate measuring and therefore time within the assessment session. Test originators have provided a manual with clear guidance on scoring and definitions. Additionally this measure has normative data for comparison (Redmond, Crane, & Menz, 2008).

Interpretation. A score of around +4 is considered normal in adult feet. Greater positive values tend towards a pronated foot type with scores of greater than +10 considered potentially abnormal. Negative values of greater than -3 are considered potentially abnormal (Redmond, et al., 2008).

Limitations. Whilst the originating article claims high inter-rater and intra-rater reliability (Redmond, et al., 2006) not all authors have concurred (Cornwall et al., 2008). However, inter-rater reliability procedures in Cornwall et al.'s (2008) study included 3 physiotherapists, two of whom had only one hour instruction and practice of the measure prior to partaking in the study when the originating authors clearly indicate the much greater level of practice required to achieve efficacy. The researcher would therefore debate their strong conclusions of “extreme caution” particularly in research use. Other authors have found good intra-rater (0.93 – 0.94) and moderate inter-rater (0.79) reliabilities in paediatric groups aged between 7 and 15 years (Evans, Rome, & Peet, 2012; Morrison & Ferrari, 2009).

7.10 Timed Single Leg Stance

Purpose. To assess static balance ability (proprioceptive ability).

Rationale. Balancing requires a person to maintain the line of gravity within their base of support. When standing still, the body sways imperceptibly under muscular control in order to adjust for changes due to the surface (such as on public transport) or breathing for example. This is controlled by proprioceptive mechanisms. Postural sway is controlled by the brain using the “ankle strategy” and poor control requires adjustments higher in the body (Gatev et al., 1999). An increased postural sway may indicate reduced proprioceptive ability and this may be associated with an increased risk of injury (Payne, Berg, & Latin, 1997).

Furthermore, it has been suggested that in a single leg balance position, medio-lateral adjustments resemble those in the single leg stance phase of gait (Pintsaar, Brynhildsen, & Tropp, 1996) and high levels of variation in postural sway in both this and the antero-lateral direction have been found to be predictive of ankle sprain (Hiller, Nightingale, et al., 2011; Nilsson et al., 2012; Wang et al., 2006).

Ability to balance statically has been shown to correlate with postural sway in a normal population (Enkelaar et al., 2013) and to correlate with ankle joint function (Pintsaar, et al., 1996).

Interpretation. The mean of the three scores was analysed. Greater ability to maintain the position and so achieve a longer time is associated with better proprioception.

Limitations. The vast majority of reviews into the efficacy of balance testing concerns older populations (such as (Langley & Mackintosh, 2007)), it is therefore difficult to apply when this study used a younger population. Additionally, no clinical cut-off levels have been identified in the literature to classify performance (Arnold et al., 2009).

7.11 **Hypermobility and Dyspraxia Scales.**

Purpose. To assess for the presence of hypermobility, benign joint hypermobility syndrome and dyspraxia in adults.

Rationale. Hypermobility of the joints may contribute to the development of arthropathy in two ways: firstly, the increased laxity of tissues may reduce ligamentous restraint thereby increasing shear at the joint surfaces, and secondly the fragility of tissues associated with the condition may increase the likelihood of bleeding. In the literature hypermobility is described as a distinct entity and also as part of syndromes such as Ehlers-Danlos Syndrome (EDS) - Hypermobility type and Benign Joint Hypermobility Syndrome. The latter two are considered synonymous in the literature and a set of criteria has been identified, the Brighton Criteria, to aid clinicians in recognising the syndrome (Grahame, 2003). The most commonly utilised clinical test for the presence of hypermobility is the Beighton

score (Beighton, Soskolne, & Solomon, 1973) and more recently the 5 – point hypermobility questionnaire has been presented (Hakim & Grahame, 2003). The self-assessed 5-point hypermobility questionnaire has been shown to correctly identify the presence of hypermobility in 84% in two cohorts totalling 392 people (Hakim & Grahame, 2003). Finally the FDQ-9 adult dyspraxia questionnaire, which sometimes associated with hypermobility, was included (Clark & Simmonds, 2011; Clark et al., 2013).

Interpretation. The Beighton score has an additive score out of 9 where a score of greater of four is considered to indicate a generalised hypermobility (Grahame, 2003). The Brighton Criteria results in a dichotomised yes or no result based on the number of items in the questionnaire marked as present. These are divided into major criteria (Beighton score or the presence of arthralgia in 4 or more joints for three or more months) or minor criteria (all the others). To be classified as having EDS the following must be present:

- two major criteria
- one major and two minor criteria
- four minor criteria
- two major and a first degree relative with a confirmed diagnosis

(Grahame, 2003)

The FDQ-9 has an additive scale with each item scoring a maximum of three on a four-point Likert scale where zero was very good and 3 was very poor and for which a 21.5 out of a possible 36 cut-off has been identified (Clark, et al., 2013). See Appendix 9 for the questionnaires.

Limitations. The Beighton score does have a limitation in that a low score may be present when other joints not included in the score do demonstrate hypermobility. Additionally, the Beighton score utilised two joints associated with arthropathy in haemophilia (elbow and knee), and it is possible that those joints may have undergone some subtle accumulative motion range reduction therefore alternative methods may be more appropriate. As there is overlap between these testing methods and no gold-standard choice in the literature particularly for PWH, the researcher has taken this opportunity to compare between scores in a mixed cohort.

The researcher also acknowledged that the FDQ-9 has not been validated for paediatric populations however there is no alternative that would not have added to the assessment time and so inconvenience of paediatric participants. It is also possible that paediatric participants would have a better recollection for questions of childhood performance and so they were asked to complete the questionnaire to the best of their ability.

7.12 Single Leg Squat Test (SLSq)

Purpose. To identify persons presenting with gluteal muscle deficits in a clinical environment without the use of EMG or other expensive equipment.

Rationale. Alterations in control mechanisms around the pelvis could change foot patterning in gait and thereby loading. The most common form of dysfunction at the pelvis is derived from poor muscular control. In particular a weakness of the gluteus medius muscle is not well tolerated in the gait pattern (van der Krogt, Delp, & Schwartz, 2012). The SLSq test has been shown to correlate well with good function of the gluteus medius muscle. Originators of the test reported excellent to

substantial inter- and intra-rater agreement (87% - 73%, $k = 0.800 - 0.613$) and it was concluded that the test may be used to identify people with hip muscle dysfunction (Crossley et al., 2011).

Interpretation. A visual holistic assessment of performance was graded as poor, fair or good. The scoring is shown in Table 7.2.

Limitations. The researcher was unable to locate any independent assessments of this test. There are many articles reviewing the efficacy of a single leg squat manoeuvre however none used the protocol and scoring system described by Crosslet et al.(2011). A procedural limitation may be the requirement to video the test which may not be possible in all clinic situations (external to the study) and so may not meet the researcher’s criterion of ensuring high clinical utility.

Table 7-2 Rating Criteria for the Single Leg Squat Test (Crossley, et al., 2011)

	Criterion	To be rated “good”
A	Overall impression across the 5 trials	
	- Ability to maintain balance	Participant does not lose balance
	- Perturbations of person	Movement is performed smoothly
	- Depth of squat	The squat is performed to at least 60° of knee flexion
	- Speed of squat	Squat is performed at approximately 1 per 2 seconds
B	Trunk posture	
	- Trunk/thoracic lateral deviation or shift	No trunk/thoracic lateral deviation or shift
	- Trunk/thoracic rotation	No trunk/thoracic rotation
	- Trunk/thoracic lateral flexion	No trunk/thoracic lateral flexion
	- Trunk/thoracic forward flexion	No trunk/thoracic forward flexion
C	The pelvis “in space”	
	- Pelvic shunt or lateral deviation	No pelvic shunt or lateral deviation
	- Pelvic rotation	No pelvic rotation
	- Pelvic tilt (take note of depth of squat)	No pelvic tilt (take note of depth of squat)
D	Hip joint	
	- Hip adduction	No hip adduction
	- Hip (femoral) internal rotation	No hip (femoral) internal rotation
E	Knee joint	
	- Apparent knee valgus	No apparent knee valgus
	- Knee position relative to foot position	Centre of knee remains over the centre of the foot

7.13 Ankle Plantarflexion Strength and Endurance Test (calf raise test)

Purpose. To detect signs of plantarflexor weakness.

Rationale. Empirical weakness of ankle plantar flexion has been noted in people with ankle HA which has also been demonstrated isokinetically (Stephensen, et al., 2012). Weakness in the ankle plantarflexors could alter the gait pattern by reducing push-off efficacy and failing to control the forward progression of the tibia over the foot in stance thereby altering ground reaction forces and potentially altering internal joint forces. It has been shown that altered plantarflexor muscle activity at the push-off phase will affect hip muscle recruitment and increase the overall energetics of gait (Lewis & Ferris, 2008). It has also been suggested that weakness of the plantarflexors could alter quadriceps muscle activation both increasing rectus femoris activation and reducing the vasti muscles' activity (van der Krogt, et al., 2012). Kinetics and kinematics have been shown to be altered in gait in children with haemophilia (Stephensen, Drechsler, et al., 2009; Stephensen, et al., 2012). However, there is evidence that reduced plantarflexor strength is not related to increased risk of acute ankle injury (Payne, et al., 1997; Wang, et al., 2006). Notwithstanding this, the researcher concluded that a clinical test for plantarflexor strength was necessary in order to determine if reported plantar flexor weakness correlated to the presence of HA. There are few plantarflexor strength tests in the literature with high clinical utility and only one with normative data: the heel-rise test. It has been determined that for an outcome of normal strength to be assigned, 25 heel-rise repetitions should be achieved (Lunsford & Perry, 1995). However, special advisors for haemophilia and podiatry recommended that 20 repetitions was a more realistic goal for a haemophilia cohort.

Interpretation. The number of successful heel lifts was counted.

Limitations. Although this motion is functional, the cross applicability to the function of the calf muscles in gait is unknown.

7.14 Human Activities Profile

Purpose. To indirectly assess the overall aerobic cardiovascular fitness of the participant.

Rationale. “Overall fitness” was a suggested Delphi factor reaching consensus. It is the researcher’s view that fitness could be said to consist of the body’s ability to respond appropriately to activity whether that is part of average daily activity, chosen leisure-time activity or extraordinary situations. It requires aerobic and anaerobic fitness, as well as strength, power and good muscular coordination. It also requires good nutrition, sleep and other aspects. In the current study it is not feasible to measure all of these aspects for a variety of reasons ranging from trying to incorporate too many variables, access to specialised equipment and safety considerations. Some aspects of strength and coordination are being covered by previous tests. The Human Activity Profile (HAP) survey provides clinicians with an indicator of aerobic fitness without having to resort to clinical testing. The estimated VO₂ max required for a list of activities has been estimated. The score has been validated against VO₂ max (Pearson correlation 0.83, p<0.01). The originator’s article provided a method of converting the test score to VO₂ max estimates using a regression equation (Daughton et al., 1982). The survey includes activities using energy expenditures ranging from 1 to 10 METs (Metabolic Equivalent of Task) and has been found to have good construct validity (Davidson & de Morton, 2007). Activities designated as high intensity have a MET value of six and greater (Slade Royall et al., 2008). Again, as with hypermobility, this self-administered survey

measure will be contrasted with the clinical Tecumseh step aerobic fitness test (see following). The test can be found at Appendix 10.

Interpretation. The highest number activity marked as “still doing” is recorded to provide the maximum score. The adjusted score is calculated by subtracting the number of activities marked as “stopped doing” from the maximum score.

Limitations. This survey provided a self-perceived estimation of aerobic fitness only and so results may be biased depending on the reliability to the participant’s responses.

7.15 Grip Test

Purpose: To indirectly assess the strength of the quadriceps muscles.

Rationale: Quadriceps muscle strength and function is important to many activities such as using stairs. Additionally, it has been shown that muscles proximal to the ankle may become weaker following ankle sprain (Bullock-Saxton, et al., 1994) and this could include the quadriceps muscles. It has also been reported to be a common finding in adult PWH (Brunner et al., 2013). Directly testing the quadriceps muscles requires either expensive or large pieces of equipment. Therefore an indirect and inexpensive method, grip strength, was chosen. This has been shown to have high test-retest reliability (Bohannon & Andrews, 2011) and is correlated to knee extension strength (Katzmarzyk & Craig, 2002).

Interpretation: The mean of both scores was taken for each arm. Normative data do not exist for average muscle strength due to factors such as muscle strength phenotypes therefore results were only compared between groups.

Limitations: The test could give an inaccurate result if the participant did not try their hardest. Therefore verbal encouragement was used to facilitate effort.

7.16 Tecumseh Step Test

Purpose: To assess the sub-maximal aerobic capacity (fitness) of an individual.

Rationale: “Overall fitness” was raised in the Delphi study as discussed in 7.14. Its relation to the development of HA could derive from the relationship of reduced fitness and fatigue. It is feasible that fatiguing quickly during active tasks may result in reduced neuromuscular control and increased injury risk. Fatigue has been noted to increase injury risk in adults in a number of sports specific situations (Emery, 2003). Cardiovascular fitness is part of overall fitness. There are numerous ways of measuring this in the clinic using minimal equipment including walk tests (e.g. 6-minute walk test) and step tests. For the purposes of this study, preference was given to step tests as they required less space and minimal equipment. Possibly the most well known of these is the Harvard step test which requires the participant to step up and down on to a 44cm step for 5 minutes at 100 beats per minute (Yuan et al., 2008). However, expert advice held that this may have been too physically taxing for the haemophilia cohort and may have challenged the ankle joint too much. The Tecumseh step test (Montoye et al., 1969) uses a lower step at 24cm for 3 minutes duration at 96 beats per minute. Normative data are available from the age of 10 to 69 years.

Interpretation: The number of heart beats in 30 seconds was recorded and compared to available normative tables which can be found in Appendix 14.

Limitations: The test provides a sub-maximal measure of fitness or aerobic capacity only and does not indicate a participant’s overall aerobic capacity which may only be determined with laboratory testing. There is the possibility of measurement error with counting the heart rate by hand however commercially

available devices provide an overall heart rate and were not suitable for this purpose.

7.17 Foot & Ankle Ability Measure (FAAM)

Purpose: To assess the perceived level of function of the ankle and foot.

Rationale: Several of the physical factors raised in the Delphi infer a reduction in function to some degree. Therefore many of the tests detailed above specifically assess for the presence of reduced performance in these areas. However, the researcher had empirically noted that objective and perceived function, do not always tally and so it was felt that a self-reported tool would help understand any relationships between clinical and self-reported function. The tool needed to be validated across numerous conditions due to the range of ankle conditions acceptable under the inclusion criteria. The FAAM (Martin et al., 2005) consists of a 21-item activities of daily living (ADL) subscale and an 8-item Sports subscale. There are also global measures of ability given as a percentage of function. The tool has been found to be reliable, valid and responsive (Carcia, Martin, & Drouin, 2008; Martin, et al., 2005). Development and validation processes involved people from the age of 8 and up indicating its use in adults and children (Martin, et al., 2005).

Interpretation: This tool provides five results: two percentages calculated from the subscales, two global percentage scales one from each subscale and a categorical response. In all scores given as percentages, higher scores represent greater function with 100% being normal.

Limitations: The researcher found that this tool was well supported in the literature (Shultz et al., 2013).

7.18 Cumberland Ankle Instability Tool (CAIT)

Purpose: To assess if perceived instability indicates membership of the haemophilia ankle group.

Rationale: Residual ankle “instability” following an initial ankle sprain has been posited to be a factor in developing a recurring problem. However, there is some debate in the literature regarding the nature of this instability whether it is mechanical (ligamentous insufficiency), functional (proprioceptive deficits) or perceived. A study has reported that perceived instability may be a better predictor of on-going ankle problems than clinical testing (Hiller, Kilbreath, et al., 2011). The CAIT is a validated tool that assesses for the presence of ankle instability. It has been reported to have good reliability (Hiller et al., 2006).

Interpretation: The score is additive and a cut-off score of ≤ 27.5 (Hiller, et al., 2006) indicates the presence of an unstable ankle in a CAI population.

Limitations: As with all self-reported tools, there may be an element of recall bias.

7.19 Conclusions

This Chapter has presented the selection of the tools included in the assessment battery. It has demonstrated the deliberation and care taken with the choices. Great care was also taken with the management of the data generated. For all of the questionnaires and tests requiring calculations, scannable forms and electronic databases were utilised to reduce the likelihood of human error.

The next two chapters present the specific preliminary work alluded to in 7.2 and 7.8. It was necessary to determine the most efficacious application of one test, the SEBT, and the testing method for exploring the Delphi activity - derived factors. Continuing to develop the case-control study protocol required an assessment of

the possibility of investigating factors pertaining to exercise and activity, and the corollaries thereof, such as injury and rehabilitation. Development of a tool to address these factors is presented in the next Chapter.

Chapter 8 Development of a Physical Activity Questionnaire for the Exploration of Historical Activity Patterns Pertaining to the Development of Haemophilic Arthropathy

8.1 Introduction

Factors raised as potentially important in the development of haemophilic arthropathy (HA) during the Delphi process included physical activity and exercise. Physical activity is a wide ranging area and could be addressed from many perspectives and in scope is broad enough for investigation independently of the other Delphi factors. However the researcher considered that to do so would be to alter the entire premise of the research programme and to abandon the working theory that the process of HA initiation was multifactorial requiring the interaction of multiple factors that were best investigated with correlations considered. Having said this much, several activity factors were raised and intuitively, one might conclude that an activity requiring great effort from the ankle joint complex might contribute to HA initiation. Therefore the researcher considered it necessary to include the subject area acknowledging that it would not be feasible within the confines of the current research programme to move beyond an initial exploration. This first exploratory step may also signpost the direction and requirements for future research into the area as well as contributing to the rounded approach to data included in the data analyses for this thesis.

The purpose of this chapter was to present the development of the tool used within the main case-control study, and to describe the decision-making processes used in the tool's design. Principles of questionnaire development are discussed in

relation to their application to the novel tool. Finally some aspects of the application of the tool are explained. The application and results of implementing the tool, which was one of a number of tools in the case-control study assessment battery, are described in Chapters 6 (application) and 10 (results and findings).

Whilst the researcher has indicated that a questionnaire was chosen to address the raised Delphi factors, consideration was given to alternative methods of data acquisition. A review of the literature did not reveal any appropriate validated tools with adequate scope with which to undertake this exploration, and so the researcher determined that there were two potential methods of approach: interviews or a questionnaire. Table 8.1 presents some of the advantages and disadvantages of these two methods.

Interview as a technique was rejected for the initial exploration as although the method would produce rich data, its scope would be unable to encompass all the factors raised by the Delphi. After due consideration, the researcher determined that a form of questionnaire would provide the most useable data in the context of restricted time, cohort size and scope of the overall study design.

Table 8-1 Questionnaire and interview advantages and disadvantages derived from Real World Research (Robson, 2011d)

<p>Pros – Questionnaire <i>The approach is relatively straightforward for the study of attitudes, beliefs, values, motives. Can be adapted to gather information from almost any type of population that is generalisable.</i> <i>High data standardisation.</i> <i>Large amount of data in a short time frame at low cost.</i> <i>Allow anonymity which can allow for ease in discussing sensitive subject areas.</i></p>	<p>Cons – Questionnaire <i>Data are affected by the characteristics of the respondents (their memory, experience, motivation etc.)</i> <i>Potential for social desirability response bias, i.e. putting answers that they think the researchers want to hear.</i></p>
<p>Pros – Interview <i>Large amount of rich data from a small cohort in a short time frame at low cost.</i></p>	<p>Cons – Interview <i>Information gathered is not generalisable.</i> <i>Data collection cannot be standardised.</i></p>

The following research questions were suggested by the physical activity, rehabilitation and occupation factor responses in the Delphi survey:

- In what ways do childhood activities and exercise influence the development of haemophilic arthropathy?
- In what ways do the level and intensity of physical effort in occupation relate to the development of haemophilic arthropathy?
- How do people with haemophilia (PWH) view rehabilitation with respect to bleed and injury management?

The questionnaire was designed to give a broad overview of these questions however it should be noted that not all data collected from this questionnaire were included in the data analyses for this thesis and as stated above will be used to inform future research.

The researcher must acknowledge that as participants are being asked to consider past events, responses may be potentially biased by recall bias including lack of memory of non-significant events.

8.2 Questionnaire Design

In the use of a questionnaire there are specific roles for the researcher and the respondent:

- Researcher: links the research questions to the questionnaire questions, framing them in such a way as to be unambiguous and yet not stray from the research questions.
- Respondent: has to understand the question, recall the information the researcher is looking for and form a judgement about it and give the answer.

(Robson, 2011d, p.253 - 254)

In settling upon the questionnaire, the starting point for design was determination of study purpose. In this case the study purpose was *to explore the possible influence of occupation, activity and rehabilitation on the development of haemophilic arthropathy using factors generated by the Delphi process*. Having determined that the factors covered by the questionnaire were to be examined in an exploratory fashion, the researcher needed to determine what type of data they wished to generate: was it going to be used to answer definitive questions or generate data requiring qualitative interpretation. Initially the researcher intended to only ask closed questions however, it was felt that the purpose of the survey would be lost without adding some open, clarifying, “why” questions. Therefore a mixed survey has been developed allowing both quantitative and some qualitative analysis which could reveal themes or patterns of behaviour. Questions then needed to be framed and structured in order to satisfy this purpose. Where possible, factors suggested in the Delphi were re-phrased into specific questions with additional open text response areas for further information.

The researcher acknowledges that the usefulness of questionnaires in an exploratory scenario has been questioned due to a perceived decontextualisation of responses in survey interviewing in that relationships between context, communication and meaning are not elaborated upon (Robson, 2011a, p.476). Whilst allowing a large amount of open-ended questions in an attempt to explore is possible, Robson contended that it is probably procedurally inefficient and ineffective taking lots of time to analyse when a questionnaire is being used. He contended that surveys work best with standardised questions where there is confidence that the questions mean the same thing to all respondents (Robson, 2011d, p.242).

In response to these considerations, the primary purpose of the questionnaire was always exploratory, aiming to move past simple description of the activities of participants, and so the time for analysis was factored in. The utilisation of a questionnaire with a mixed format was thought beneficial in that data may be gained that are both immediately useful and may inform future research. The questionnaire was pre-tested to try to ensure that the questions were understood in the same way by a disparate group of people as described in section 8.5.

8.3 Scope of Questionnaire

Table 8.2 presents the exercise, activity, rehabilitation and occupation factors raised by the Delphi that were included in the questionnaire.

Table 8-2 Exercise, Activity, Rehabilitation and Occupation Factors Derived from the Delphi & Included in the Historical Activity Questionnaire

Age - developmental maturity
Age – growth spurts
Faulty exercise/activity training methods
Growth stage and appropriate activity
History of injury
Lack of protective equipment for chosen activity
Level/intensity of physical activity
Occupational choices
Physical activity choices
Poor adherence to rehabilitation programmes
Surfaces used for exercise purposes

The scope of the questionnaire was limited to these factors and closely related complementary questions that would help explain the original factor. Either the factor was simply transformed into a question, for instance “Surfaces used for exercise purposes” became a list of surfaces with the request that participants identify all that they have used. Others required supporting questions or being broken down to sub-questions that would lead to more holistic information. So for “Growth stage appropriate activity” the researcher needed to know what the participants were doing, at what age, for how long and at what intensity. These additional questions allowed some contextualisation of responses.

Whilst the researcher attempted to restrict questions strictly to the Delphi factors it became apparent during the design phase and following initial piloting that additional questions were needed in some instances. For instance in “poor adherence to rehabilitation”, it was necessary to ascertain if rehabilitation had been offered in the first instance.

8.4 Question Design

Questions on a questionnaire should reflect the goals of the study and in particular answer the research questions. A good questionnaire:

- Provides a valid measure of the research questions
- Gets the cooperation of the respondents
- Elicits accurate information

(Robson, 2011d, p.253)

With respect to the first item, as the research questions were exploratory, it was not intended that the overall questionnaire would represent a single valid measure of the propensity of activity to influence arthropathy development. However, within the questionnaire, specific questions, in particular those addressed by means of a visual analogue scale (VAS – see below), can be considered to be a valid measure of that question.

Wording of all the questions was crucially important both to gain cooperation and accurate information. Recommendations on question design include keeping them simple and short. Also avoiding double-barrelled questions, leading questions, negatively framed questions and only asking questions where the respondents will have the answers (Robson, 2011d, pp.255 - 256). Questionnaire appearance is also crucial; it should appear spacious with room to include full answers (Robson, 2011d, p.259).

Question types can be closed ended (fixed-alternative, VAS, Likert scales) or open ended. Several types of closed ended questions were utilised in this questionnaire. Fixed-alternative questions were used to explore how certain actions or activities came to be. Fixed-alternative question responses should be accurate, exhaustive,

mutually exclusive and on a single dimension (Robson, 2011d, p.254). VAS' were used preferentially where possible as the ratio data allowed the use of more robust analysis techniques. Finally questions with dichotomised answers – Does your chosen activity require protective gear? – were used. Examples of the former two questions used are shown in Figures 8.1 and 8.2.

11, Please tick all the exercise/training/activity surfaces that you have used.

Grass (level playing field)	<input type="checkbox"/>	Grass (uneven)	<input type="checkbox"/>	Dry slope	<input type="checkbox"/>
Paving (tarmac/concrete/stone)	<input type="checkbox"/>	Ice/snow	<input type="checkbox"/>	Astroturf	<input type="checkbox"/>
Other uneven surfaces	<input type="checkbox"/>	Sprung flooring	<input type="checkbox"/>	None	<input type="checkbox"/>
Rubberised track	<input type="checkbox"/>	Wooden floors	<input type="checkbox"/>		
Ash courts	<input type="checkbox"/>	Water	<input type="checkbox"/>		

Figure 8-1 Example of A Fixed-Alternative Question

5, How much physical effort or energy has been needed to carry out your main or longest lasting occupation?

Figure 8-2 Example of a Visual Analogue-Type Question from the Adult Questionnaires

Robson (2011) placed firm emphasis on the importance of the conceptual framework for, or purpose of, the questionnaire when investigators are attempting to add context to closed, descriptive data. This is where the researcher's pragmatic-realist approach of trying to identify a set of possible mechanisms and the context in which they operate came into play. This prevented the questionnaire from deviating from its purpose by adding questions that would be of interest to the researcher but not actually relating to the Delphi factors. Questions were in fact

added outside the listed Delphi factors but this was in response to pre-testing feedback.

8.5 Pre-Testing

Pre-testing or piloting is essential in questionnaire development.

Recommendations suggest an initial informal stage for constructive feedback on wording and layout from purposive friends or colleagues (Robson, 2011d, pp.264 - 265). Followed by utilising representatives of the target group who are asked to complete the questionnaire but also to give any thoughts on wording, clarity of intention, and other comments such as extraneous questions or obvious omissions (Robson, 2011d, pp.264 - 265).

Pre-testing for this questionnaire took place solely in the host haemophilia centre and was purposive. The pre-testing process undertaken for this questionnaire is presented in Table 8.3.

Table 8-3 Pre-Testing Process for the Activity Questionnaire

Stage	Participants & mode of recruitment	Purpose	Participants Comments
1	Supervisory team and special advisors N = 4	Group discussion. Face validity. Layout and structure. Clarity. Overall comments. Omissions/extraneous questions with respect to Delphi factors.	Separation into adult and young person, and haemophilia and non – haemophilia versions. It was thought that adding a “not applicable” could result in haemophilia groups skipping questions. Addition of non-organised activities. Addition of option of having undertaken no physical activity ever.
2	Lay people. Purposive sample of centre administrators and friends. N = 4	Completed questionnaire - informal verbal and written feedback on wording, layout, omissions.	Further improvement to layout. Clarity of two questions.
3	Haemophilia centre clinicians. Purposive: differing professions N = 3	Face validity. Wording, layout, omissions/extraneous questions. Verbal and written feedback provided.	Recommended addition of question. Concern over complexity and understanding of use of VAS scales.
4	People with haemophilia recruited from a single clinic by Consultant N = 3	Completed survey. Face validity. Wording, layout, omissions/extraneous questions. Verbal feedback provided.	Responses to 3 questions not as expected. Concern over survey lengthiness and complexity of historical exercise aspects. Therefore these aspects were altered.

Participants at all stages of the questionnaire pre-testing were given an explanation of the purpose of the questionnaire and how to complete it including visual instructions in how to complete a VAS-type question. As the questionnaire was exploratory, participants were informed that they could ask questions if they were unsure of any question or answer as there was no grading of the test. Participants for the lay- and clinician-testing stages of the pre-testing were identified on the basis of pragmatic factors such as time available to give the questionnaire due consideration and likelihood to return it with feedback on time. Participants for

stages two and three had one week to complete and return the feedback to the researcher; some just provided written feedback whereas others added further oral explanation to their written comments. The questionnaire was updated according to feedback at each stage. The PWH participants were identified during a single clinic and agreed to stay for a little longer to complete the questionnaire and offer feedback. The PWH participants were asked to complete the questionnaire at their own speed with the researcher present who informally noted the time taken as part of the development process. Then feedback was collected by the researcher both verbally and from written notes and directives on the prototype questionnaires.

The historical physical activity/exercise component of the survey was particularly important as it may have reflected on several of the Delphi factors and also on the findings of the clinical side of the assessment. The researcher therefore closely reviewed what was being asked in this question in consideration of the feedback that this was a time-consuming question and difficult to recall the required detail. Moreover, the purpose of collecting the extensive historical data included in early versions was considered. The researcher decided that she had fallen into the trap of collecting too much data and that it was not important to know in detail about every exercise choice but just about the ones most often undertaken or for a reasonable duration. Participants were still asked to record as much of their regular formal and informal physical activity as they could remember but using a simpler format based on the Bone-Specific Physical Activity Questionnaire or BPAQ (Weeks & Beck, 2008). Following this they were asked for more detail on their top five (or less if they felt that there were not five) activities. The adult haemophilia questionnaire was finalised after eight iterations and questionnaires for the non-haemophilia and paediatric groups were derived from this. A completed

questionnaire is attached (Appendix 11) and the others are attached electronically as eAppendices 24-26.

Table 8.4 presents the final list of paraphrased questions together with the mode of enquiry.

Table 8-4 List of Paraphrased Questions Included in the Historical Activity Questionnaire for Adult Haemophilia Participants. *VAS = Visual Analogue Scale

Question	Enquiry Mode
School leaving age	Fixed alternative list
Occupations with duration	Free text list
Reason for currently not working	Fixed alternative list
How active longest lasting occupation/school	VAS*
How much effort for longest lasting occupation/school	VAS
Historical activity/exercise	Free text list
For (up to) 5 most frequently undertaken activities – frequency of participation	Free text
- Where it occurred (for organised versus casual)	Free text
- Level of competition	Free text
- History of injury	Free text
- Cause of injury	Free text
For the most frequently undertaken activity, how did they learn it	Fixed alternative list
What kind of exercises surfaces	Fixed alternative list
Was protective gear required for favourite sport	Dichotomous yes/no
Frequency of using protective gear	VAS
History of unreported minor injuries	Yes/no
Reasons for not reporting	Free text
Was rehabilitation offered	VAS
Was rehabilitation completed by participant	VAS
Reasons for not completing rehabilitation	Free text
Did participant recall playing the same games as their peers	Fixed alternative list
Were some games not allowed	Fixed alternative list
Who controlled selection of activities	Fixed alternative list
Did the participant recall being as active as their peers at age 5	Fixed alternative list
- Age 10	Fixed alternative list
- Age 15	Fixed alternative list
Any final comments	Free text

8.6 Sampling Procedure Considerations

This section discusses the issues of sampling from the perspective of application of the finalised questionnaire in the case-control study.

A sampling frame is the population from which participants for a study are drawn such as the electoral roll or in this case the full list of PWH in each participating centre. Random sampling from within the sampling frame is the most advantageous method as it precludes many types of sampling bias such as how much of an influence the selection will have on the variables under investigation (Robson, 2011d, pp.270 - 277). This was not possible for this questionnaire as the sample population was the same as for the case-control study and so was not random. The current questionnaire sample is considered to be a non-probability sample. In this type of sample it is considered that a statistical generalisation may not be made beyond the sample surveyed (Robson, 2011d, pp.270 - 277).

Participants for the questionnaire were drawn from the participating haemophilia centres. Whilst the researcher was in the position to access the complete clinic list for participating sites, specific inclusion and exclusion criteria were in place for the case-control study of which the questionnaire was a part. The sampling in this study is therefore also considered purposive as the participants had to meet the inclusion criteria. This approach is commonly used within flexible designs (Robson, 2011d, pp.270 - 277). Therefore as random sampling was precluded on two fronts: sample frame and inclusion criteria, it is possible that some sampling bias may be present as those being questioned had already agreed to take part in the full study.

8.6.1 Sample size

It has been recommended that about 100 data sets per major subgrouping in a survey should be collected (Borg & Gall, 1989). The intention in the application of the study was to collect 90 that is, falling short of this recommendation. However, the researcher did not consider this an issue as the questionnaire was exploratory

and there were limitations on potential recruits. Moreover, the researcher ensured that the assumptions for statistical tests being applied to data derived from specific questions of the questionnaire were met. Part of the decision on sample size was decided for the researcher by the population under consideration. The host haemophilia centre (which is considered a large centre) has a population of 430 PWH of whom only a small number meet the inclusion criteria for the key group. The overall study recruitment was 90 participants of whom 60 were PWH and 30 were normal volunteers; this is actually quite a large haemophilia study group.

The researcher acknowledges that the group size and inclusion criteria may have led to selection bias and so attempted to ameliorate this and improve the potential to generalise results by trying to recruit a deliberately heterogeneous population.

The age range was a broad spread from twelve to fifty years. Further, the investigator sub-divided the age range into five year blocks and tried to recruit approximately equal numbers into each group. Additional steps taken to try to reduce recruitment bias were to recruit from multiple sites and to ensure that participant's underlying haemophilia clinical presentations were (within the inclusion criteria) as broad as possible in terms of residual factor levels, numbers of bleeds experienced and treatment regimens.

8.7 Coding and Analysis

The results of the study are presented in Chapter 10. As the intention was to apply the questionnaire to those already taking part in the remainder of the study, there was no data quality issue resulting from a low response rate.

8.7.1 Coding

Differing coding techniques were applied depending on the question type. These are displayed in Table 8.5.

Table 8-5 Coding applied to various question types.

Closed questions: VAS	Closed questions: fixed alternative	Open response support questions	Historical exercise spreadsheet	Historical exercise detail questions
Measurement in cm from left hand anchor of scale. Ratio data	Numeric coding assigned. Nominal data	Thematic analysis.	Activities listed and grouped. Period of participation noted. Nominal and ratio data	Data were coded into ordinal scales. Injury status was dichotomised and thematic analysis for injury reason.

Thematic analysis of open questions entails some loss of information (Robson, 2011d, p.267) but was necessary for the overall purpose of the research study to be met. The simplified themes were then coded. It is advisable to not use codes based on early responses as these could be not characteristic of the full cohort but of a set of representative respondents (Robson, 2011d, p.267). Therefore, coding began after 50% of respondents had been recruited into each group.

8.7.2 Analysis

The survey was developed with versions for PWH and non-PWH and also paediatric versions. Various versions were deemed necessary as a special advisor suggested that having “not applicable” options for areas such as occupation might result in questions being skipped. This means that certain questions were omitted from certain questionnaires: occupational questions for paediatric versions and bleed-related questions for non-haemophilia versions, raising issues with analysis.

This was dealt with by simply having a reduced number of responses entered into analysis for those questions. Additionally, these questions were not going forward to regression analysis introducing no issues with regards to the statistical assumption for number of data points per variable entered. Details of statistical analysis can be found in Section 10.7.

8.8 Conclusion

The structure and contents of this questionnaire were wholly based on the results of the Delphi process making its applicability unique to this research study. As the purpose of the questionnaire was exploratory, formal validity testing was not required. However that did not preclude ensuring a robust pre-testing phase to make certain that the questionnaire served its purpose. In the next Chapter, the second piece of preliminary development work for the case-control study protocol in which the efficacy of the SEBT is further investigated is presented.

Chapter 9 Development of a Study-Specific Protocol for the Star Excursion Balance Test – An Electromyographic Study

9.1 Introduction

The Delphi results suggested that proprioceptive deficits may have the potential to influence the development of HA. It was also suggested that biomechanical control of the lower limb may be important and this can be affected by proprioceptive abilities. Proprioception is the ability to sense, locate and orientate one's body and its parts in space (Konradsen & Voigt, 2002). It has two facets kinaesthesia and joint position sense. The former is the ability to sense the motion and position of the parts of the body using sensory organs (proprioceptors) found in muscles and joints. The latter is the ability to perceive the position of a joint without visual assistance. Some sources separate the ability to balance and maintain equilibrium from kinaesthesia citing the latter's focus on the body's motion or movements, while proprioception (balance) focuses more on the body's awareness of its movements and behaviors (Konradsen & Voigt, 2002).

In this chapter, a study is presented investigating the potential to tailor the Star Excursion Balance Test (SEBT) specifically to address factors raised in the Delphi. A brief review of the SEBT is given to explain its selection for this study, followed by the study protocol and results. These results are then discussed and a study-specific protocol presented.

9.2 Brief Review of the Star Excursion Balance Test

There are many ways of measuring proprioceptive components. Some use highly complex laboratory equipment such as force plates and perturbation platforms. However, it is the intention of this research programme to only use tests with good clinical utility. There are many validated tests in the literature and in particular several balance tests have been designed with an elderly population in mind in the area of falls prevention (Sherrington & Lord, 2005). However, the likely demographic for this research programme is much younger and fitter and so it was felt that a more challenging and dynamic test would be required.

The Star Excursion Balance Test (SEBT) has been described as a functional test that quantifies lower extremity reach while challenging an individual's limits of stability (Olmsted, et al., 2002). It looks for sensorimotor deficits whilst challenging strength and motor co-ordination. The test as originally described requires the participant to stand in the centre of a grid, barefoot with hands-on-hips, and reach as far as possible along one of eight test directions, touch down lightly and return to the centre. The anterolateral reach direction is demonstrated in Figure 9.1.

Participants first practice the technique and then reach distances are recorded. Reach distances are normalised to the participant's leg length. An aggregate score can be recorded by adding all reach distances and taking the mean or specific distances can be reviewed reflecting the specific challenge intended by the test (see below and discussion) (Olmsted, et al., 2002).



Figure 9-1 Star Excursion Balance Test with anterolateral reach direction demonstrated

As the test challenges hip, knee and ankle motion and control, the researcher considered that the test could also be said to examine lower limb biomechanical efficacy. The tool has been shown to be reliable (Hertel, 2000) and be able to detect impairments between healthy and injured individuals, and also within subject differences for injured to non-injured side (Hertel et al., 2006; Hubbard, et al., 2007) for a variety of lower limb injuries (Gribble, Hertel, & Plisky, 2012). A minimally clinical important difference (MCID) of 6- 8% normalised reach has been suggested (Plisky et al., 2006) and a 4cm difference in a single reach direction was used in one study as the MCID (Olmsted, et al., 2002).

However, the full testing procedure as originally described is lengthy. Due to this studies have been undertaken looking at streamlining the procedure by identifying any redundancy in the testing directions (Hertel, et al., 2006) and number of practices required to reach stability of reach distance (Robinson & Gribble, 2008). The original protocol recommended six practice reaches in each of the eight test directions and three recorded trials on both legs (Olmsted, et al., 2002). Combining

the outcomes of the redundancy and stability trials resulted in a streamlined version using three reach directions, with four practices and three recorded trials. It has become custom to select the anterior, posteromedial and posterolateral reach directions with articles either recommending (Gribble, et al., 2012) or using this combination (Hubbard, et al., 2007; Plisky, et al., 2006). The researcher considers that this selection of reach directions may have occurred inadvertently as the source of this information is always given as either Hertel 2008, a review article, in which the author quotes his own earlier study: Hertel et al. 2006. It should be noted that the originating 2006 article was specifically assessing for the presence of chronic ankle instability (CAI) and stated that anteromedial, medial and posteromedial were of most relevance to the detection of CAI and at no point is any other specific testing protocol recommendation made. However, the Hertel 2008 article does indeed make the recommendation citing the 2006 article as the source. The researcher has not found other sources demonstrating that the anterior, posterolateral and posteromedial protocol is universally best placed to detect all pathologies or for all study purposes. It should be noted that the remaining reach directions are: anterolateral, lateral, posterior. The researcher has seen no evidence precluding the selection of an alternative reduced protocol based on the specific needs of the study population.

Earl and Hertel (2001) suggested that reach directions could be individually selected for specific rehabilitation purposes to better focus interventions if they were to be shown to recruit leg muscles differently and also to require different motion at the ankle and knee. Therefore they looked at the activity of six lower limb muscles during the SEBT using surface electromyography (sEMG) together with

the maximum excursion of the knee and ankle joints. Significant differences in the activity between all muscles tested except gastrocnemius were found to indicate that muscle activity was direction dependent (Earl & Hertel, 2001).

Selecting a reduced protocol that also challenged muscle groups which are currently thought to be key in controlling the lower limb may help to identify some redundancy allowing future rationalisation. The researcher considered gluteus medius (GMd) and gluteus maximus (GMx) among the key muscles in the context of this research but these have not been previously investigated in the SEBT.

Therefore the purpose of this exploratory investigation was to identify any differences in the directional activity of GMd and GMx muscles when performing the SEBT in a healthy cohort using sEMG to allow an informed choice of reduced protocol which would maximally challenge both lower limb balance and control.

9.3 Methods

9.3.1 Protocol overview

The full study protocol and participant information sheets can be found at eAppendices 27 and 29. In order to understand the activation of the gluteal muscles for use with PWH, it was first necessary to establish baseline activation with a healthy population group. With the exception of recording the reach distances, the protocol of Earl and Hertel 2001 was replicated in order that the results could be considered an extension of their study. It was considered that the reach distances were irrelevant to the aim of the study, moreover, in the above study, although reach distances were recorded, they were not reported upon.

In this study design, it is necessary to have a maximal sEMG level with which to compare the levels recorded during the SEBT, and this is achieved using a

maximum voluntary isometric contraction (MVIC). In many studies commercially available systems such as the Quantitative Muscle Assessment system are used (Meldrum et al., 2007) however the researcher did not have access to this system and was time restricted, and so chose to follow suit with Earl and Hertel by using exercise-derived measures. Boren et al. (2011) examined the gluteal muscle activation patterns for 22 gluteus medius-specific and 22 gluteus maximus-specific exercises and the researcher selected the exercises that demonstrated the greatest activation on sEMG and used the same exercise protocol (Boren et al., 2011). All SEBT reach directions were used with a reduced practice protocol as per Robinson et al. (2008).

9.3.2 Participants

Twelve healthy normally active adults volunteered for the study (4 men and 8 women, age = 21.5 years, range 18 - 30). Participants were recruited from the Physiotherapy Programme at the University of Brighton. Criteria for exclusion included any history of major injury to the lower limbs, any current painful condition affecting the lower limb, any recent head injury or condition that could affect balance. Informed consent was taken and the study was covered by the overall study ethical approval from the University of Brighton.

9.3.3 Procedures

All participants received instructions in the same manner. The procedure for measuring the MVIC for GMd and GMx was demonstrated first prior to the SEBT procedure being explained. After this the sEMG electrodes were affixed in line with recommendations from SENIAM (Hermens et al., 2006). The electrode positioning is shown in Figure 9.2. Using sEMG requires careful electrode application and

attention to the recording details to ensure that no crosstalk is being recorded or that there are no movement artefacts (Kamen & Gabriel, 2010). Participants indicated which leg they would choose to balance on whilst kicking a ball and this was used as the test leg.



**Figure 9-2 Electrode positions:
1 = GMd and 2 = GMx**

For the MVICs of the two muscles, exercises were selected that had previously been demonstrated to produce maximal contractions (Boren, et al., 2011). These are shown in Figures 9.3 and 9.4. Participants practiced the exercise prior to performing three repetitions holding each for a five-second count, ensuring adequate rest to prevent fatigue prior to testing. Verbal encouragement was given to urge the participant on.

The SEBT was performed barefoot with the hands on the hips. The foot was placed centrally over the crossing point of the reach directions (Olmsted, et al., 2002) see Figure 9.1. To practice the SEBT, participants performed four practice trials moving around the template in the following order: Lateral, Anterolateral, Anterior, Anteromedial, Medial, Posteromedial, Posterior and Posterolateral. Directions were labelled with respect to the balancing leg. For data collection, one

reach consisted of the participant reaching as far as possible, touching down lightly, returning to the centre and placing the reach foot on the floor. Reaches were discarded if the participant placed the foot firmly down in the reach, lost balance or took their hands off their hips. As the purpose of this study was to collect EMG data the trial reach distances were not recorded. Participants performed recorded reaches moving around the template in the same order as described above but reaching three times in each direction before moving on to the next.



Figure 9-3 Maximal Voluntary Isometric Contraction exercise for GMd: Side plank with upper leg lift. EMG reading taken from lower leg

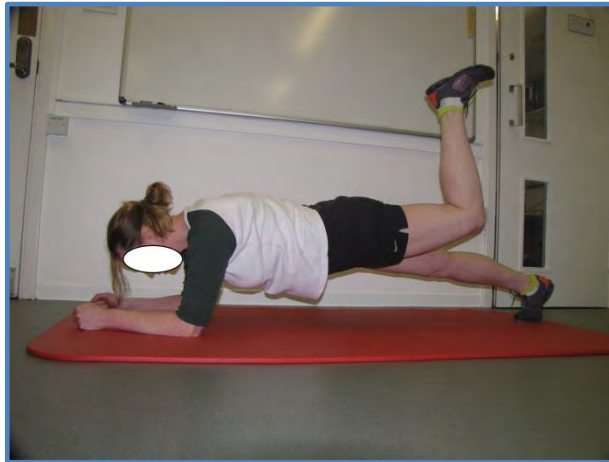


Figure 9-4 Maximal Voluntary Isometric Contraction exercise for GMx. Plank with unilateral flexed knee and hip extension. Reading taken from the lifted leg.

9.3.4 Data Processing

SEMG data were collected during both the MVICs and SEBT and processed using MATLAB (v. R2012a) software. The raw data were low-pass filtered at 300Hz and high-pass filtered at 20Hz. These settings are in line with SENIAM recommendations (Hermens, et al., 2006). Also due to the laboratory construction a filter was used to eliminate background mains frequency effects at 45 - 55Hz. The raw data were full wave rectified. A moving average (MAV) function was applied to the data using a 50-sample window. The average MAV value was calculated about a 1-second window during the peak MVIC for each muscle. For the SEBT reach directions an average MAV was calculated in each direction for each muscle for a 10-millisecond window about the peak of contraction. The smaller window was necessary due to the differing speeds at which participants performed the trials (Earl & Hertel, 2001). The average MAV value for each muscle for each trial was normalised to its respective MVIC value. This was the dependent variable.

An example of the raw sEMG is attached as e-Appendix 30.

9.3.5 Statistical Analysis

A review of the data using the Shapiro-Wilk test and boxplots indicated that the distribution was not normal and so a Friedman's test (non-parametric) was performed for each muscle. Where significant results were found, post hoc analysis with Wilcoxon signed-rank tests was conducted, with a Bonferroni correction applied, which was used to identify significant differences between specific reach directions. The significance level following Bonferroni correction was set at $p < 0.0125$. The statistical analysis was carried out using Excel (Microsoft 2000) and SPSS (IBM SPSS v20) software.

9.4 Results

Significant differences in the EMG activity for both GMd and GMx were found ($p = 0.0005$ for both muscles). Figure 9.5 shows the normalised sEMG activity for GMd and GMx during the different reach directions. Median and Inter Quartile Ranges of normalised sEMG activity for each reach direction is presented in Table 9.1.

There was a statistically significant difference in the activity of the GMd muscle depending on reach direction, $\chi^2(2) = 26.139$, $p = 0.0005$. There were statistically significant differences in the activity of GMd between the reach directions of Posterior and Anteromedial ($Z = -2.748$ $p = 0.006$), Posterior and Anterolateral (-2.510 $P=0.012$), Posteromedial and Anteromedial ($Z = -2.510$ $p = 0.012$), Posteromedial and Lateral ($Z = -2.903$ $p = 0.004$) and Posterolateral and Lateral ($Z = -2.510$ $p = 0.006$). There were no other significant differences for GMd between the other reach directions following Bonferroni correction.

There was also a statistically significant difference in the activity of the GMx muscle depending on reach direction, $\chi^2(2) = 27.722$, $p = 0.0005$. There were in addition statistically significant differences in the activity of GMx between the reach directions of Posterior and Anterior ($Z = -3.059$ $p = 0.002$), Posterolateral and Anterior ($Z = -2.746$ $p = 0.006$), and Medial and Anterior ($Z = -2.981$ $p = 0.003$). There were no other significant differences with this muscle.

Figure 9-5 Normalised sEMG activity for the gluteus medius (GMd) and maximus (GMx) muscles in all 8 reach directions (Post = Posterior, PM = posteromedial, PL = posterolateral, Med = medial, Lat = lateral, Ant = anterior, AM = anteromedial and AL = anterolateral)

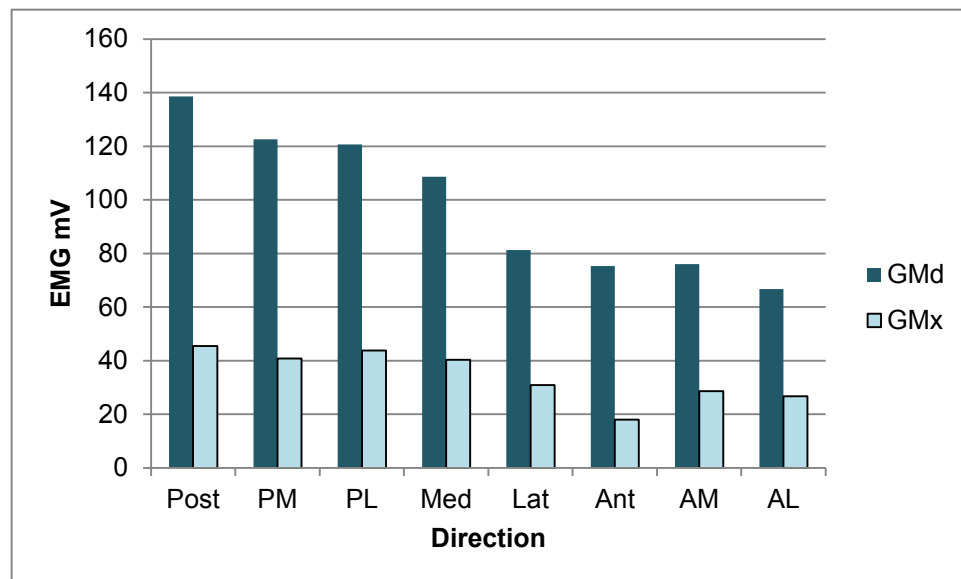


Table 9-1 Descriptive Statistics: Interquartile ranges for EMG activity of Gluteus Maximus (top table) and Gluteus Medius (bottom table).

1a	N	Percentiles		
		25th	50th (Median)	75th
Post-GMx	12	15.5584	37.1904	68.9868
PM-GMx	12	17.2717	35.2948	66.5860
PL-GMx	12	14.0434	37.3758	51.4467
Med-GMx	12	27.3688	39.3452	49.6531
Lat-GMx	12	12.7025	25.1178	53.7276
Ant-GMx	12	10.9107	14.1563	25.3113
AM-GMx	12	9.5745	20.5690	34.4273
AL-GMx	12	13.0084	18.7608	27.4613
1B	N	Percentiles		
		25th	50th (Median)	75th
Post-GMd	12	59.5367	107.1627	260.2516
PM-GMd	12	54.0145	95.6924	207.4706
PL-GMd	12	32.0444	100.7137	195.6320
Med-GMd	12	38.1249	125.3361	159.7749
Lat-GMd	12	47.1274	79.2038	121.5226
Ant-GMd	12	26.2250	64.8021	134.0562
AM-GMd	12	21.4213	66.5682	123.5802
AL-GMd	12	29.0175	67.2095	102.1282

*Key: Post = Posterior, PM = posteromedial, PL = posterolateral, Med = medial, Lat = lateral, Ant = anterior, AM = anteromedial and AL = anterolateral.

9.5 Discussion

This study presents the sEMG activity of the GMd and GMx muscles during the SEBT for the first time. The activity of these muscles was direction dependent and

in general was greater with reach directions to the posterior and in the medial direction. Directionality has also been demonstrated for vastus medialis, vastus lateralis, medial hamstrings, biceps femoris and tibialis anterior muscles. However, the gastrocnemius muscle would appear to act independently of direction (Earl & Hertel, 2001).

The posterior reach direction elicited the greatest sEMG activity for both gluteal muscles. In the case of GMx this may be due to the forward lean position of the trunk in performing this task. In this position the body's centre of mass is moved ahead of the hip joint. Therefore, greater GMx activity is generated to counteract the higher hip flexion torque required to counterbalance the increased external hip flexion torque (Reiman, Bolgla, & Loudon, 2012). However, overall the GMd means are much larger than their GMx equivalents. For instance, in the posterior reach direction GMd mean is 107.16mV whereas GMx is 37.19mV. GMx is a much larger muscle in terms of cross-sectional area and it might be thought would produce a greater amount of force in the SEBT. This might have several explanations. The amplitude of sEMG signal drops markedly with distance and with amount of subcutaneous fat present and it is possible that this affected detection. Other factors affecting force-EMG relationship include: muscle length at recording, joint angle, design and placement of electrodes, speed of contraction, and muscle fatigue (Kamen & Gabriel, 2010). In this study the joint angles would vary from person to person depending on their technique for reaching as there was no restriction apart from retaining hands on hips. However, the researcher considers that there should have been no effects from fatigue as in some participants the greatest sEMG output was during the final reach. It is also possible that GMx is simply not required to activate as strongly to maintain stability in the positions

taken up in the SEBT, however the researcher considers this unlikely as a primary function of the muscle to control forward lean positions of the trunk (Wilson et al., 2005). It cannot be determined which of these factors is responsible for the large difference between means but the researcher considers that the first suggestion of greater subcutaneous fat increasing the distance between the electrode and motor point might be key.

The researcher chose to use the MAV of the raw data as opposed to the root mean square (RMS) which is perhaps more commonly seen (e.g. (Earl & Hertel, 2001)). This was chosen as it has been suggested that MAV provides optimal EMG amplitude detection and processing (Clancy & Hogan, 1997; Phinyomark et al., 2013). Another difference between this study and several of the papers utilising EMG with SEBT is in the choice of statistical tests where several have chosen ANOVA as part of their statistical analysis package. In this study, the results were not normally distributed and so a Friedman's test was chosen. It has been stated that in general, sEMG signals present a non-Gaussian (normal) amplitude distribution and that these amplitude distribution characteristics are not dependent on the muscle investigated, nor on the type of contraction or force level tested (Bilodeau et al., 1997). The researcher wonders how much results can be relied upon where authors have not indicated that results were checked for normality of distribution.

When using the SEBT during the case-control study, consideration must be given to the purpose of including it in the clinical assessment battery. Potential factors that may contribute to the development of HA being considered during this study include proprioception, strength and ankle dorsiflexion. If previous research is

married with current results then an SEBT protocol that best fits all of the above should be possible. It has been confirmed that the test does not lose efficacy by reducing the number of reach directions or the protocol for practice and recorded trials (Hertel, et al., 2006; Robinson & Gribble, 2008).

Studies such as Plisky et al. (2006) used this reduced testing protocol. These authors carried out a prospective study of 235 high school girls and boys who played basketball. In boys a right to left anterior reach difference of greater than or equal to 4cm was significantly associated with injury. Authors concluded that athletes with an anterior right/left reach difference were 2.5 times more likely to injure themselves. Authors also suggested that SEBT may have increased sensitivity for detecting injury risk due to not only testing balance but also strength and co-ordination (Plisky, et al., 2006).

It would therefore appear that an acceptable reduced protocol consists of 3 reach directions, with four warm-up practices and three test trials could be used in the case-control study.

9.5.1 Selecting a test protocol for the case-control study

Using the results from this study and the published literature it is possible to select an SEBT protocol that reflects the purpose in selecting it as a measurement tool.

The results of the current study suggest that, in order, posterior, posterolateral, posteromedial and medial reach directions elicit the greatest sEMG outputs from GMd and GMx. It is also known that GMd function can be negatively impacted following an acute ankle sprain (Bullock-Saxton, et al., 1994). So, if a single direction is chosen from current results the most important muscle to consider might be GMd and posterior the most apposite direction. GMx dysfunction has not

to the researcher's knowledge been associated with increased likelihood of sustaining an ankle sprain or of dysfunction post-sprain but may affect control of DF and control of knee extension in gait via the bi-articular effect of muscles as it links with gastrocnemius (Schenau, 1989). This occurs via the coupling of joint moments where hip extension leads to knee extension via rectus femoris acting with a fixed length, and knee extension leading to ankle PF via a non-elongating gastrocnemius muscle. The combination of these two force couples means that energy is transferred from proximal to distal via a fixed knee position and effecting an ankle PF force (Jonkers, Stewart, & Spaepen, 2003; Schenau, 1989). It may also be co-contracting in order to help stabilise the pelvis on the hip to prevent lateral hip drop using its abductor fibres (Grimaldi, 2011; Wilson, et al., 2005). The posterior reach direction is also the greatest sEMG output for GMx. Therefore, from the current research the posterior reach direction was selected.

In terms of identifying the presence or absence of a condition, the directions of anteromedial, medial and posteromedial were recommended as most strongly correlated to the presence of CAI (Hertel, et al., 2006), pathomechanical aspects of which may be relevant in the development of HA. Furthermore posteromedial was the most representative reach direction in terms of performance for all conditions tested. Again selecting a single reach direction based on this study, it would seem appropriate to add the posteromedial reach direction to the proposed protocol.

Finally, the SEBT could be utilised to indirectly assess for quadriceps strength. The Earl and Hertel (2001) results suggested that vastus medialis and vastus lateralis worked hardest in the anterior reach direction. Furthermore they determined that anterior, anteromedial and medial reach directions produced more ankle DF than

all other directions. It would therefore seem appropriate to select anterior as the third reach direction to challenge the quadriceps muscles and the ankle joint.

9.6 Conclusion

Research continues to clarify the efficacy of the SEBT. This study has demonstrated the activity of the GMd and GMx muscles during the SEBT which will enhance the ability of clinicians to make an informed choice in deciding to select a reduced reach direction protocol. The reach directions of posterior, posterolateral, posteromedial and medial elicit the greatest sEMG response from the gluteal muscles. Using these results and the published evidence, the researcher set the following protocol for the case-control study: anterior, posterior and posteromedial reach directions; four practice trials and three recorded trials. A description of the procedure for the SEBT as applied in this study was given in section 7.8

This Chapter concluded the design and development elements of the case control study which required careful consideration of multiple elements from condition prevalence, the pool of potential participants, the most efficacious way of assessing for factors and the acceptability of the test protocol. The researcher considers that all possible attention was paid to ensure both the efficacy of the assessment protocol in terms of its efficiency at performing the tasks for which it was designed and also with regards to acceptability to the participant and investigators. Evidence of this foresight is presented in terms of the successful data collection and analysis of 90 data sets. The results and findings of the data collected in this study are presented in the next Chapter.

Chapter 10 Main Study: Evaluation of the Effect of MSK and Exercise Factors on the Development of Joint Disease in Haemophilia - Results & Findings

10.1 Introduction.

A case-control study was carried out evaluating the effects of a number of musculoskeletal factors intrinsic to the body, and exercise factors on the development of haemophilic arthropathy at the ankle. This involved comparison between three groups of individuals who presented in the following ways: haemophilia with ankle joint disease (HmAk), haemophilia with no joint disease (HmC) and normal volunteers (NV). The study design and development has been described in Chapters 6 – 9. This chapter focusses on presenting quantitative data analyses of factors capable of predicting membership of the haemophilic arthropathy at the ankle group.

In this chapter the data analysis process is outlined first. Following this the data are explored and participants described. Between groups univariate analysis is then presented followed by the process by which factors were chosen for regression analysis. The regression analysis is described next and finally an exploration of activity data collected by the historical activity questionnaire is presented. A summation of the chapter with key points draws the presented information together.

10.2 Data Analysis Overview

Factors identified via the Delphi Process and reduced in number following a feasibility review, were investigated in a case-control study using clinically based measures which have been fully described in Chapter 7. The data collection generated a large number of data sets and multiple data types (i.e. continuous, ordinal and categorical data). Some of the continuous data sets were not normally distributed due to their nature, such as scores with a percentage-based outcome where 100% represented “normal”. There were occasional missing data points for some variables due to various reasons such as a participant opting not to perform one test or errors in a completed questionnaire received from a satellite site that could not be corrected in time. In order to ensure clarity and due to the complexity of the analysis, procedures are described in turn as they were utilised. All data analyses was carried out using SPSS v22 (IBM SPSS V22) and Microsoft® Office Excel® 2010.

Several statistical tests were utilised during data analyses, for ease of text perusal, the reporting style for each test is as follows:

- Chi Square test of association - χ^2 (degrees of freedom), test statistic, p -value. E.g. $\chi^2(8), 11.558, p=.172$
- Mann-Whitney U test - U test statistic, z = standardised test statistic, p -value. E.g. $U = 741, z = .743, p=.457$
- ANOVA - F (between groups degrees of freedom, within groups degrees of freedom) = F -distribution, p -value. E.g. $F(2, 87) = 3.599, p = .031$
- Tukey, Games - Howell and Dunne post hoc tests, p -value reported.

- Pearson and Spearman correlation tests r or $r_s = X$; p -value. E.g. $r = .823$; $p = .0005$.

Appendix 13 presents a full glossary of the statistical tests used in this Chapter.

10.3 Initial Data Exploration

10.3.1 Participants

Ninety people participated in this study. They were divided equally into three groups with 30 members in each group. Table 10.1 details their demographics.

Table 10-1 Participant demographics. All data are presented with means and standard deviations.

	Haemophilia Ankle	Haemophilia Control	Normal Volunteers
Age (years, SD)	28.77 ± 7.36	26.73 ± 8.97	32.62 ± 9.43
Age range (years)	15.96 – 47.52	15.21 – 49.18	14.53 – 50.49
Weight (kg)	78.98 ± 13.40	73.63 ± 13.55	75.51 ± 13.49kg
Height (cm)	177.42 ± 14.02	175.64 ± 9.55	177.04 ± 8.02

Age matching was considered but, due to the small pool of potential participants, this was not feasible across all groups however an attempt was made to broadly age match. Whilst an ANOVA showed a significant difference in age between groups ($F(2, 87) = 3.599, p = .031$), this lay between the HmC and NV groups ($p = .026$); there was no difference between the haemophilia groups. However, the researcher considered this to be unimportant as test results show that the 6 year difference (NV older) in means was not reflected in a comparable difference in performance in the data sets. Eight ethnic backgrounds were reported across the groups and are displayed in Figure 10.1. This broadly reflects the urban locations of the participating centres.

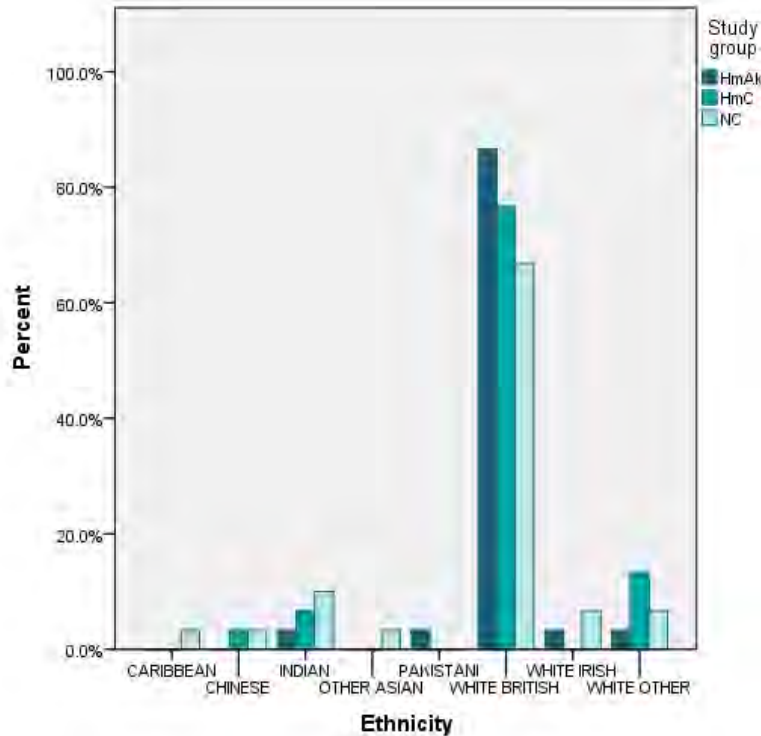


Figure 10-1 Ethnic diversity of study group. HmAk = Haemophilia Ankle, HmC = Haemophilia Control, NV = Normal Volunteers

10.3.2 Education and Occupational Data

Age at which education ceased is presented for the groups in Figure 10.2. A Chi square test shows that there was no difference between groups ($\chi^2(8), 11.558, p=.172$). A wide range of occupations were submitted by those working. Some of the student participants completed occupation questions and others chose not to. Participants were asked to identify the occupation of the greatest duration and identify how much physical effort was required and how active they felt the work to be on visual analogue (VAS) scales. Some participants who were still studying also completed these questions with regards to their school life and their data were included.

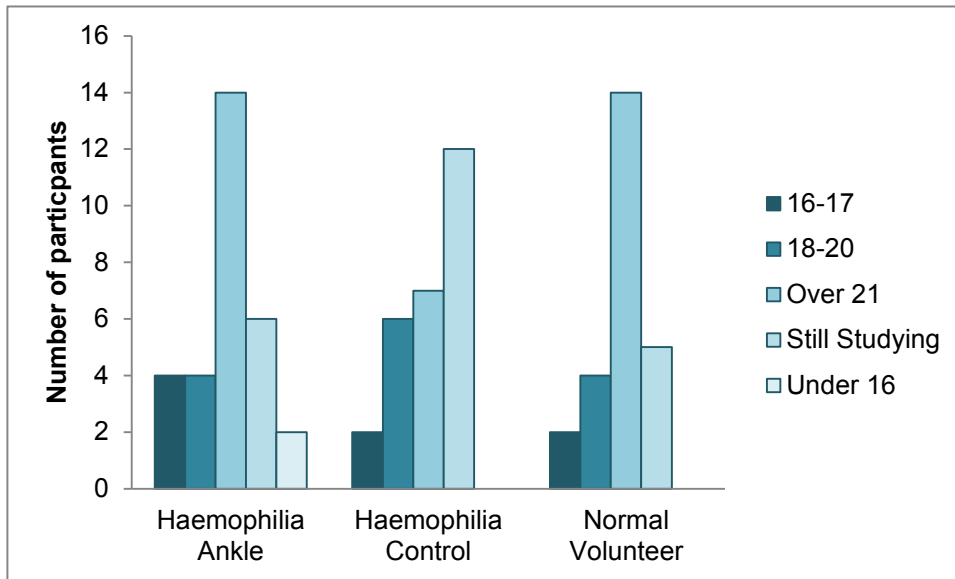


Figure 10-2 Ages at which Participants Ceased Education Presented by Group

Occupations were coded as per the International Standard Classification of Occupations (International Labour Office, 2012) with “student” substituted for “military” as there was no one of that ilk in the cohort in order to include students. Table 10.2 details the occupations by group. A Chi Square test showed no differences between groups ($X^2(8)$, 12.534, $p = .129$) indicating an unlikely impact on ankle disease development. Mann-Whitney U tests were run to determine if there were differences in VAS scores with the cohort dichotomised into presence or absence of ankle joint disease, which showed that neither the occupational physical effort nor active VAS’s were significant between groups (Active VAS $U = 778.5$, $z = 21.147$, $p = .251$. Effort VAS $U = 741$, $z = .743$, $p = .457$) reinforcing the position that physical aspects of occupation did not affect group membership in this cohort.

Table 10-2 Distribution of occupations for which effort & activity data were provided as classified by the International Standard of Classification.

Haemophilia Ankle	29
Technicians	5
Student	3
Professionals	5
Clerical support	8
Sales/service	6
Skilled agriculture	1
Craft	1
Haemophilia Control	21
Technicians	3
Student	4
Professionals	6
Clerical support	5
Sales/service	3
Normal Volunteer	27
Technicians	4
Professionals	14
Clerical support	3
Sales/service	4
Elementary	2

10.3.3 Haemophilia presentation

With regards to clinical haemophilia presentation, 29/30 in the HmAk group had a baseline factor level of less than 1% indicating severe disease. In the HmC group, the presentation varied between 2 – 12%. Fifteen cases in the ankle group were bilateral where participants clearly identified the most problematic ankle resulting in 18 right and 12 left ankles being identified as the involved ankles. The same numbers of left and right ankles were randomly assigned to the other two groups for between group analysis purposes. Inhibitor status was currently negative for all haemophilia participants however 2 participants (6.67%) in the HmAk group and 6 participants (20%) in the HmC groups had a history of inhibitor status as a child.

This may be important as during the period when the inhibitor is active, it is extremely difficult to control bleeding episodes.

10.4 Univariate Analysis – Between Groups Comparison of Involved Ankles

Table 10.3 presents the tests and questionnaires used for the cohort study, along with the generated variables. Univariate analysis was carried out between groups utilising data from the nominated involved ankle. It was known that the data analysis procedure would be complex with several continuous variables known to have non-normal distribution by nature. The data analysis procedures are shown in Figures 10.3 and 10.4 for categorical and continuous data types respectively. A one way analysis of variance (ANOVA) was utilised for data demonstrating normal distribution. This is used for comparison of the means between three or more unmatched groups. Where data did not meet the assumptions for ANOVA, the non-parametric Kruskal-Wallis test was used. Both these methods merely identified the presence of a difference between groups but did not specify where the differences lie or their direction. In order to achieve this, post hoc testing was used with in the case of ANOVA, the Tukey or Games-Howell test, and for Kruskal-Wallis the Dunne test with a Bonferroni correction to account for multiple comparisons. A p value of .05 was selected.

Table 10-3 Measurement tools and resultant variables

Tool	Variable
Physical activity questionnaire	Duration of play (years) Age activity started (years) History of Injury (yes/no)
Height and weight	BMI
Anterior drawer test	Categorical scale (0 – 3)
Goniometer	Subtalar inversion (degrees) Subtalar eversion (degrees) Great toe extension (degrees)
Ankle lunge test	Ankle joint complex DF indicator (cm)
Star excursion balance test (SEBT)	Mean reach distances, anterior, posterior & posteromedial (cm) Maximum reach distances, anterior, posterior & posteromedial (cm) Total mean reach distance (cm)
Foot posture index	Additive scale indicating pronation/supination
Timed single leg stance	Eyes open mean time (secs.) Eyes closed mean time (secs.)
Brighton criteria	Categorical group membership for benign joint hypermobility syndrome
5-point hypermobility questionnaire	Additive scale for generalised hypermobility
FDQ-9	Additive scale for dyspraxia
Single leg squat test	Categorical scale for pelvic control
Calf strength test	Count of calf raises
Human Activity Profile (HAP)	Maximum additive scale Adjusted score = maximum – items stopped
Hand dynamometer	Grip strength (kg)
Tecumseh step test	Recovery heart rate (heart beats in 30 secs)
Foot and ankle ability measure (FAAM)	Additive scales (%) plus ordinal scale
Cumberland ankle instability scale (CAIT)	Additive scale (%)

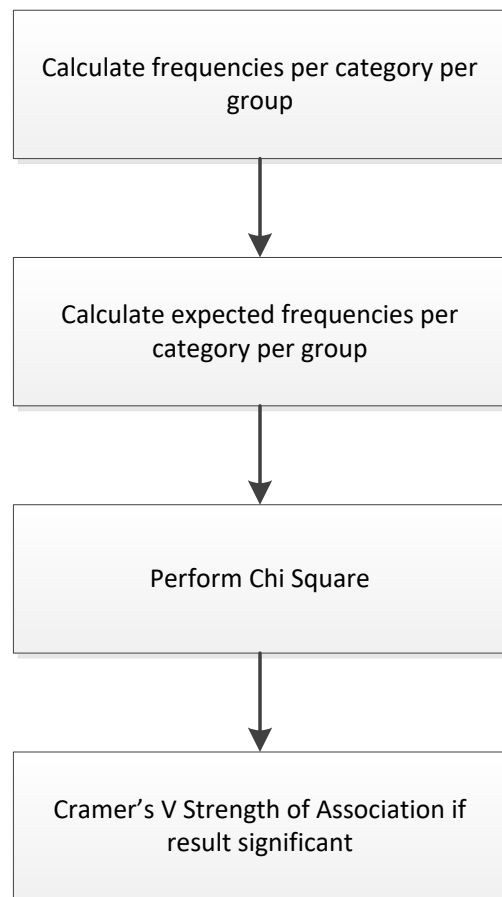


Figure 10-3 Flow Chart of the Categorical Data Analysis Process

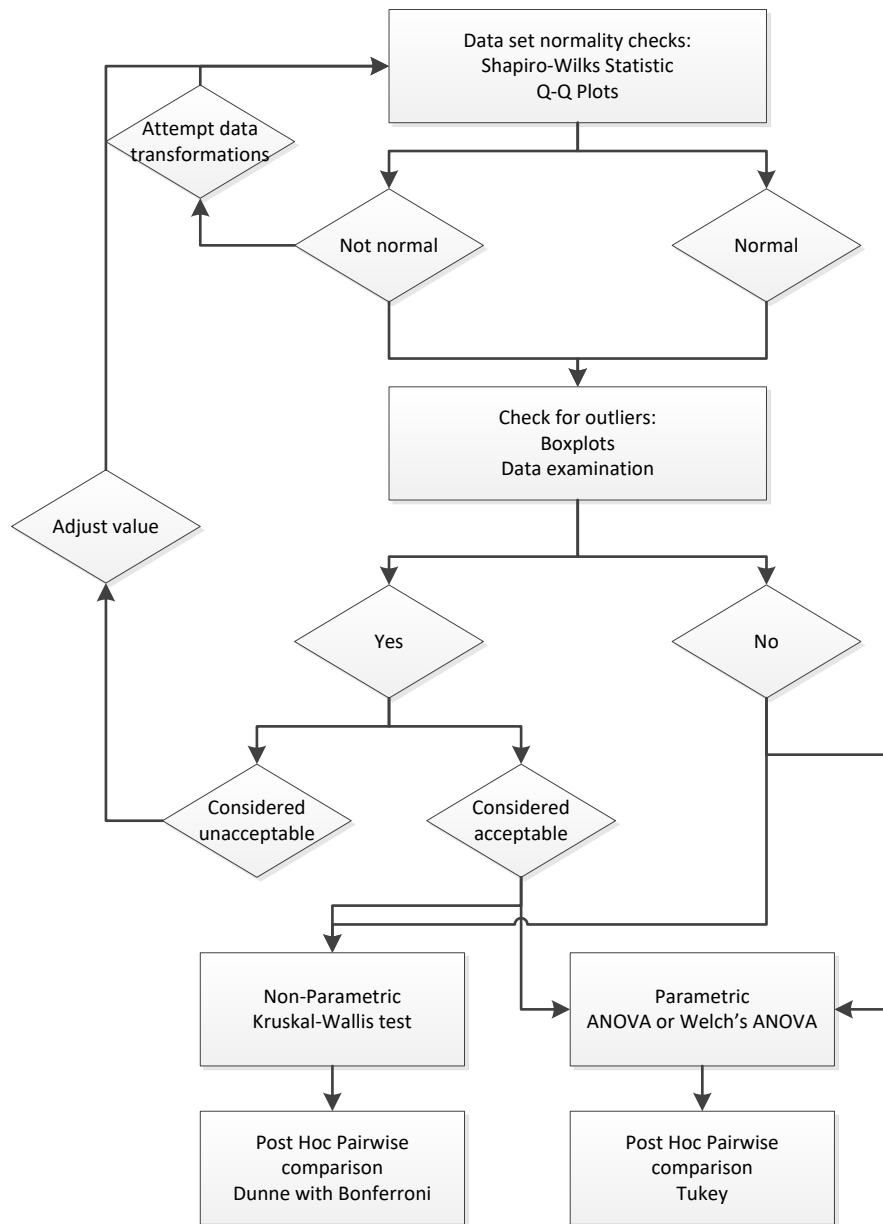


Figure 10-4 Data processing summary for continuous and ordinal data

Results for the main outcome variables are presented in Tables 10.4 – 10.7 for continuous/ordinal data and Table 10.8 for categorical data.

Table 10-4 Group Mean Comparisons: Continuous Data Sets, Involved/Sham-involved and Non-Involved/Sham-Non-Involved, & Involved/Sham-Involved sides of Haemophilia Ankle, Haemophilia Control and Normal Control, N=30 all groups.

Variables	Haemophilia Ankle		Haemophilia Control		Normal Volunteers		Between groups p value
	Involved side mean (SD)	Sham uninvolved mean (SD)	Sham involved mean (SD)	Sham uninvolved mean (SD)	Sham involved mean (SD)	Sham uninvolved mean (SD)	
Subtalar inversion	24.73 (12.69)	28.40 (12.46)	31.03 (11.90)	31.20 (10.98)	37.73 (8.13)	38.60 (8.74)	0.0005*
Subtalar eversion	13.90 (7.34)	14.20 (6.12)	14.63 (6.07)	14.70 (7.35)	19.20 (5.88)	19.90 (5.64)	0.001*
Great toe extension	42.53 (14.48)	45.23 (12.67)	44.07 (14.68)	44.77 (16.45)	44.90 (10.08)	42.67 (9.83)	0.0782
Ankle lunge test	7.23 (6.63)	10.05 (6.38)	12.70 (5.86)	12.26 (5.52)	14.19 (2.98)	13.42 (3.67)	0.002*
SEBT mean anterior	74.77 (9.54)	72.19 (6.27)	72.35 (10.82)	71.93 (8.85)	72.34 (9.05)	76.73 (11.06)	0.571
SEBT max anterior	77.75 (10.44)	74.44 (6.03)	74.34 (10.98)	74.69 (8.62)	74.98 (8.62)	80.30 (12.09)	0.380
SEBT mean posterior	77.15 (10.86)	78.81 (11.27)	72.83 (13.28)	77.08 (11.29)	77.79 (12.47)	74.54 (15.39)	0.238
SEBT max posterior	81.53 (10.51)	82.44 (11.12)	77.40 (14.25)	81.46 (11.48)	81.86 (12.55)	79.30 (14.53)	0.311
SEBT mean postero-medial	73.43 (9.56)	76.89 (10.30)	69.60 (14.05)	73.12 (12.28)	75.70 (12.30)	71.69 (12.29)	0.149
SEBT max postero-medial	77.33 (8.98)	79.93 (10.84)	72.93 (13.40)	76.91 (13.19)	79.05 (11.84)	76.63 (13.06)	0.123
SEBT overall mean	81.83 (8.72)	78.74 (11.70)	78.95 (10.50)	79.11 (9.37)	78.97 (12.77)	79.91 (9.14)	0.495
Key: SEBT = Star Excursion Balance Test. HmC & NV groups had an ankle assigned as sham involved to match the HmAk group							

Table 10-5 Group Mean Comparisons: Continuous Data Sets, Involved/Sham-involved and Non-Involved/Sham-Non-Involved, & Involved/Sham-Involved sides of Haemophilia Ankle, Haemophilia Control and Normal Control, N=30 all groups.

Variables	Haemophilia Ankle		Haemophilia Control		Normal Volunteers		Between groups p value
	Involved side mean (SD)	Sham uninvolved mean (SD)	Sham involved mean (SD)	Sham uninvolved mean (SD)	Sham involved mean (SD)	Sham uninvolved mean (SD)	
Single leg stance eyes open	46.59 (14.55)	43.64 (19.78)	50.33 (14.25)	49.92 (14.54)	51.68 (11.63)	52.77 (9.34)	0.469
Single leg stance eyes closed	6.28 (4.80)	7.10 (4.60)	8.51 (8.89)	9.32 (7.78)	8.23 (7.53)	10.93 (8.73)	0.434
Foot Posture Index Total	3.00 (5.21)	2.53 (5.44)	2.07 (4.65)	1.90 (5.12)	3.67 (2.73)	3.50 (3.20)	0.404
Calf strength	16.70 (5.38)	18.47 (3.24)	17.83 (4.30)	18.87 (3.14)	20.00 (.00)	19.40 (3.29)	0.016*
Grip strength	37.57 (7.79)	36.86 (8.59)	35.64 (9.43)	36.52 (10.50)	40.50 (9.33)	40.47 (9.94)	0.109
Cumberland Ankle Instability Tool	16.55 (13.92)	22.31 (11.61)	26.63 (8.07)	27.77 (7.36)	31.60 (9.38)	30.40 (7.80)	0.0005*
Key: *Indicates significant results							

Table 10-6 Group Mean Comparisons: Continuous Data that used Involved Side Only Measures. N=30 all groups

Involved Side Only Variables	Haemophilia Ankle	Haemophilia Control	Normal Volunteers	p value
FAAM* ADL score	82.41 (13.02)	98.06 (4.78)	98.84 (3.04)	0.0005*
FAAM ADL functional score	80.57 (15.40)	97.00 (6.64)	99.17 (3.73)	0.0005*
FAAM sport score	68.44 (18.79)	93.44 (11.56)	96.15 (10.31)	0.0005*
FAAM sport functional score	67.33 (26.71)	95.03 (8.60)	98.27 (6.47)	0.0005*
Key: FAAM = Foot & Ankle Ability Measure, ADL=activities of daily living. *Indicates significant results				

Table 10-7 Group Mean Comparisons: Continuous Data Sets that used Non-Side Dependent Measures. N=30 all groups.

Non-Side Dependent Variables	Haemophilia Ankle	Haemophilia Control	Normal Volunteers	p value
Body Mass Index	24.33 (3.39)	23.76 (3.32)	24.31 (3.53)	0.688
Tecumseh step test	36.96 (6.80)	38.55 (7.92)	36.37 (7.72)	0.727
Human Activities Profile (HAP) Maximum	80.33 (22.55)	86.07 (23.76)	92.33 (4.09)	0.0005*
Human Activities Profile Adjusted	69.40 (35.81)	77.80 (47.28)	87.50 (10.72)	0.0005*
Age key sport started	6.5 (2.85)	7.4 (3.09)	6.88 (2.97)	0.438
Duration of exposure to key sport	13.24 (6.19)	9.41(5.14)	12.72(7.18)	0.045*
*Indicates significant results				

Table 10-8 Median or Other Appropriate Comparisons: Categorical or Ordinal Data Sets, Involved/Sham-involved and Non-Involved/Sham-Non-Involved, & Involved/Sham-Involved sides of Haemophilia Ankle, Haemophilia Control and Normal Control, N=30 all groups.

Variable	Haemophilia Ankle		Haemophilia Control		Normal Control		Between groups <i>p</i> value
	Involved side median	Sham uninvolved median	Sham involved median	Sham uninvolved median	Sham involved median	Sham uninvolved median	
Anterior Drawer Test (hypomobile, normal, lax-normal, hypermobile)	Hypomobile	Normal	Normal	Normal	Normal	Normal	0.001*
Single Leg Squat Test (good, fair, poor)	Poor	Fair	Fair	Fair	Fair	Fair	.0005*
Non-Side Dependent Measures							
FAAM overall function rating (normal, nearly normal, abnormal, severely abnormal)	Nearly Normal		Normal		Normal		.0005*
5-point hypermobility questionnaire (hypermobility % yes)	23.3		13.3		23.3		.535
Beighton Score (hypermobility % yes)	29		16		33		.279^
Brighton Criteria (% meeting criteria)	30.00		36.67		30.00		.685
FDQ-9 dyspraxia questionnaire (% yes)	13		10		20		0.533^
History of injury (% yes)	60.02		45.24		33.63		.001**^

*Indicates significant results ^overall chi square result

10.4.1 Side-dependent variables

Subtalar inversion was different between groups ($p < .0005$) with post hoc testing indicating that the haemophilia groups had reduced range compared to the NV group (HmAk $p = .0005$, HmC $p = .037$). *Subtalar eversion* was also significant ($p = .001$) again with the haemophilia groups showing reduced range in comparison to the NV group (HmAk $p = .006$, HmC $p = .02$). These are an unexpected finding as it might be expected that the HmAk group alone would show a reduction in range secondary to the presence of the HA disease process. There is no published haemophilia literature regarding this which could be used for comparison.

Great toe extension was broadly comparable across groups and was not statistically significant ($p = .078$). If, as the researcher had hypothesised, the factors with potential to influence HA development were similar to those influencing ankle sprain, then a comparative increase in range might have been expected (Willems, et al., 2005). The *Ankle lunge test* was reduced in the HmAk group which was a statistically significant result ($p = .002$). Post hoc testing confirmed that the test was able to differentiate the ankle group from the others (HmC $p = .004$ & NV $p = .0005$). A reduction in DF might be expected with established ankle joint disease however reduced range has also been shown after ankle sprain (Vicenzino, et al., 2006) and failure to recover range may prove an early indicator of altered AJC function leading to prolonged altered loading.

Dynamic balance was assessed using the *Star Excursion Balance Test (SEBT)*. The mean and maximum reach distances were used for analysis of each SEBT reach direction. Additionally an overall mean score was calculated. None of these data sets were statistically significant. This is unexpected as reduction in balance

control has been reported in haemophilia cohorts (Fearn et al., 2010). This was also the case with the static balance *Single Leg Stance Test (SLST)* with eyes open and eyes closed ($p = .469$ eyes open, $p = .434$ eyes closed), however the mean scores do indicate that the HmAk were not performing either SLST test as well as the other groups. Of more interest, despite the lack of significance, was that the mean scores indicated that the HmAk group were better at performing the SEBT than the other groups. This result might be due to previous balance training from rehabilitation. A comparison was made between the mean and maximum reach distance scores which established that strong correlations existed (e.g. for Anterior reach: $r = .979$, $p = .0005$) indicating that in the ongoing study just the maximum reach need be recorded. The *Foot Posture Index* has indicators for foot motion in the three cardinal planes and the researcher decided to explore the individual measures to see if there were differences within the foot based on planes of motion however this was not the case and so the total score is reported here. This too was unremarkable ($p = .404$) with mean scores across the groups of between 2.07 and 3.67 which are within the normal value range for the test (Redmond, et al., 2008).

Calf strength was reduced in the HmAk and HmC groups ($p = .016$) this was confirmed with post hoc testing (HmAk $p = .04$, HmC $p = .037$). This result along with the subtalar range of motion results may represent unique changes in the haemophilia cohort. The researcher is unable to account for the presence of these differences in the absence of arthropathy. A reduction in calf strength may reflect persistent altered exercise exposure throughout life although that is not reflected by the self-reported historical activity data reported later in this chapter. *Grip strength* was not significant between groups ($p = .109$). This test is an indirect

assessment of quadriceps muscle strength and the result is different from published haemophilia literature that has shown a reduction in isokinetic knee extensor strength in haemophilia populations (Stephensen, et al., 2012). This difference may be due to testing methods.

The *Cumberland Ankle Instability Tool* (CAIT) was able to distinguish between groups with the HmAk group having a lower score ($p = .0005$), post hoc pairwise comparison confirmed this ($p = .0005$). All domains of the *Foot and Ankle Ability Measure* (FAAM) questionnaire produced the same result. This is in keeping with other investigations of ankle problems that have indicated that self-perception may be a stronger indicator of dysfunction than currently available clinical or laboratory testing (e.g. (Wikstrom et al., 2010)).

10.4.2 Non-side-dependent variables

The results of the *BMI*, *Tecumseh step test*, *Beighton score*, *5-point hypermobility score*, *FDQ-9 dyspraxia questionnaire* and “*Age key sport started*” were found not to be significant. The results of the BMI and Tecumseh Step test are broadly comparable with the haemophilia literature. The presence of an elevated BMI in haemophilia children has been variously reported. Schoenmakers et al. (2006) found no evidence in a large paediatric cohort whereas Douma-Van Riet et al. (2009) noted a small increase in prevalence. Along with these authors, the researcher considered that the reports in the literature do not indicate a serious concern with regards to high BMI. Submaximal fitness assessment, as represented by the Tecumseh Step Test, is not directly comparable to the haemophilia literature where maximal fitness testing has been reported. The Tecumseh step assessed a fitness range which was not challenging for the cohort. The test is graded from

outstanding to poor and the majority of participants in each group achieved the outstanding grade (see Figure 10.5 and Appendix 14 for detail of the grading system). The other fitness assessment utilised in this study, the *Human activities profile* (HAP), covers a range of activities requiring a larger range of aerobic fitness levels. There was a significant difference between groups for both the maximum and adjusted scores ($p = .0005$) with the adjusted score able to distinguish the HmAk group ($p = .001$); that is cardiovascular fitness had an impact on group membership and that the HmAk group's fitness was reduced at included activities requiring a higher fitness. This is not in keeping with some reported fitness studies in haemophilia paediatric populations where $VO_2\text{max}$ derived from a bicycle ergometer test was found to be comparable with healthy peers (Douma-Van Riet et al., 2009; Van Der Net et al., 2006). The difference may be explained by the age range of the current study.

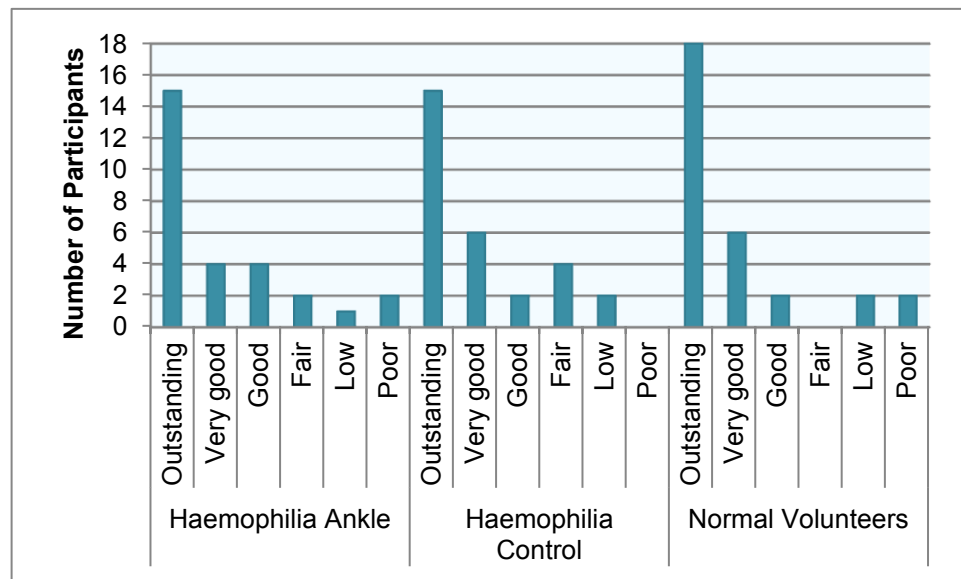


Figure 10-5 Tecumseh Step Test Results.

The researcher had suggested that primary hypermobility might be an important factor in the development of HA at the ankle however this has not been borne out in between groups' analysis using any of the chosen measures. However, the number of participants in each group who can be classified as hypermobile should be considered. Grahame (2003) suggested that a score of 4 or greater out of a possible 9 is indicative of the presence of joint hypermobility. Furthermore the population prevalence of hypermobility in British children has been reported as 10.5% (Clinch et al., 2011). The population prevalence for the overall cohort is 27% which is well in excess of this figure. Within the groups the percentage of participants with generalised hypermobility was roughly equivalent in the HmAk (29%) and NV (33%) groups, but it was lower in the HmC group (16%). This may be a relevant finding with regards to influencing the development of HA. However, this result is not statistically significant even though there are twice as many people in the HmAk group with a Beighton score of 4 or greater than in the HmC group. The most common joint to present a positive finding was the 5th metacarpophalangeal joint at 35.6% which is slightly higher than the 29% reported in a large UK paediatric study (Clinch, et al., 2011). The presence of Benign Joint Hypermobility Syndrome as assessed by the Brighton criteria was not statistically different between groups. Finally the FDQ-9 which assesses for the presence of dyspraxia was not significantly different between groups. There is no haemophilia literature pertaining to this subject. Dyspraxia has been associated with the presence of hypermobility (Clarke, 2012) and the researcher considered that clumsiness and poor co-ordination as a child have been might be indicative of the potential to sustain more injuries and thereby influence HA development.

The “duration of play of key sport” was significant between groups but on pairwise comparison only the difference between HmC and NV groups was significant ($p = .036$). However the age that the activity was begun was not significant. Sustaining an injury during sport was also significant with a Chi Square showing $X^2(2), 14.688$, $p = .001$ and with a very strong effect, Cramer’s $V = .411$, $p = .001$ (Cohen, 1992). In the context of HA, this may indicate the necessity of injury prevention.

The final two tests were significant but the researcher considers that they are potentially reflecting the result of the disease process rather than recognising underlying differences between groups. The *anterior drawer test* showed that the HmAk group were stiffer than the others (HmC $p = .088$ & NV $p = .003$). Finally the *Single Leg Squat test* of pelvic control was significant with a moderate association (Cramer’s $V .382$, $p = .0005$). This test, from the researcher’s observations where performance was poor in the HmAk group, was actually showing the participant’s compensations to restricted ankle DF rather than reflecting pelvic control.

Returning to the CAIT, which distinguished the HmAk group, a cut-off point is available in the literature for chronic ankle instability. A score of less than or equal to 27.5 indicates the presence of instability (Hiller, et al., 2006). The researcher therefore considered it important to see if the same cut-off applied to this HA in order to enhance its clinical applicability. A Mann-Whitney test confirmed that there was a significant difference between a dichotomised cohort divided into those with ankle problems and those without, $U=1629.5$, $z=6.325$, $p = .0005$. As the researcher considered it more important to identify those with ankle disease than to correctly identify those without, the sensitivity score was the focus. Analysis of the ROC (receiver operating characteristic) curve and analysis of point co-ordinates indicated that the best cut off point would give a sensitivity of 87% and a specificity

of 77% which corresponded to a score of 25.5. Analysis of area under the curve (AUC) of a ROC graph gave 0.905 (C.I. .834 - .976) indicating an excellent performance (see Figure 10.6). Therefore for the CAIT score, a cut-off of 25.5 appears to give good indication of ankle group membership.

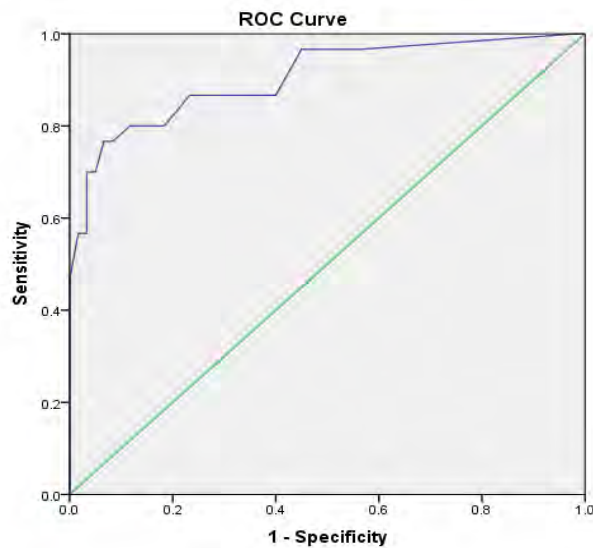


Figure 10-6 ROC curve for Cumberland Ankle Instability Tool used for the identification of haemophilic arthropathy at the ankle.

A worked example of data analysis using the CAIT is in Appendix 15.

10.5 Identification of Factors for Regression Analysis

The purpose of this study has always been to determine factors with a degree of explanatory significance. Therefore although various types of data reduction techniques were available such as cluster analysis or principal component analysis (PCA), they did not enable the researcher to meet this aim either due to the nature of the procedure (cluster analysis has no explanatory component) (StatSoft, 2016) or because the study did not meet assumptions (PCA requires a minimum of 150

data sets and this study only had 90 available) (Lund Research, 2013). Therefore a regression process was utilised.

The choice of independent variables (IV) will influence regression results. It performs best when IVs correlate with the dependent variable (DV) but not with each other. A goal is to predict the DV with the fewest possible IVs where each IV predicts a substantial portion of the DV. Also, if a future goal of research is to manipulate the DV it is worthwhile selecting IVs amenable to intervention. “An optimal set of IVs is the smallest reliable, uncorrelated set” that encompasses all measured domains affecting the DV (Tabachnick & Fidell, 2014b). Reduction in number of factors was also required from the “ratio of cases to IVs” rule of thumb for regression analyses described in the section 10.6. Advice from a statistician indicated that there is no single way of approaching this; a multi-faceted iterative process was recommended. This implied some subjective bias in the process. The remaining factors were therefore sorted into thematic domains in order to differentiate between measures representing aspects of complex Delphi factors such as “altered biomechanics of the lower limb affecting the foot and ankle”. The researcher therefore identified factors for entry into regression based on statistical significance, represented domain, analysis of factor association (as indicated by Pearson’s or Spearman’s correlation), researcher experience and extant published literature. The results of this reasoning process are presented in Table 10.9.

Table 10-9 Selection process for factors to be developed into the regression model.

Domain	Potential factors	Between groups P value	Statistical association if applicable	Theoretical relevance	Selection
Foot & ankle range of motion (ROM)	EVERSION	.001	Eversion & inversion related: $r=0.631, =0.0005$	Limits in subtalar motion would require compensation in adjacent joints potentially increasing ankle load.	No
Foot & ankle ROM	INVERSION	.0005	See above	Limits in subtalar motion would require compensation in adjacent joints potentially increasing ankle load.	Yes
Foot & ankle ROM	ANKLE LUNGE TEST	.002	No significant relationships	Ankle DF has been shown to remain limited post - injury and could affect foot ankle loading and likelihood to re-injure.	Yes
Cardiovascular (CV) fitness	HUMAN ACTIVITY PROFILE – all measures	.0005	All HAP - closely related, $\rho = 1.0, P=0.01$	Overall fitness may influence fatigue during activity and likelihood to injure. HAP adjusted differentiated HmAk from other groups.	Yes
Lower Limb strength	CALF STRENGTH	.016	No significant relationships	May affect gait patterning: deceleration of the tibia over the talus and achieving full knee extension mid-stance altering ankle load.	Yes
Functional ability	FOOT & ANKLE ABILITY MEASURE – all	.0005	All FAAM are closely related, $\rho = 0.876, P=0.0005$.	FAAM sport subscale represents activities requiring highest function & differentiated HmAk from other groups.	Yes
Ankle stability	CUMBERLAND ANKLE INSTABILITY TOOL	.0005	CAIT & FAAM, closely related, $r=.730, P = .0005$	Self-perception of function has been shown to be an accurate predictor of chronic ankle instability & differentiated HmAk from other groups.	No
Exercise/activity patterns	DURATION OF EXPOSURE	.045	Duration & History related, $\tau_b=-.183, P = .05$	Exposure to activities has been linked to likelihood of injury.	Yes
Exercise/activity patterns	HISTORY OF INJURY	.001	See above	Injury history could indicate persistent MSK deficiencies.	No
Proprioception	SEBT POSTEROMEDIAL MAX	.123	No significant relationships	It would appear logical that good dynamic balance and control would aid improved performance in many activities thereby lessening the likelihood of injury	Yes
Foot & ankle ROM	GREAT TOE EXTENSION	.078	No significant relationships	Has been linked to likelihood of spraining ankle.	No

10.6 Regression Analysis

Regression is a flexible approach particularly useful in real world situations that are not amenable to reductive experimental design (Tabachnick & Fidell, 2014b).

Section 10.5 identified factors that would be included in the regression processes.

These were:

Subtalar joint inversion	FAAM-sport subscale
Ankle lunge test	Duration of exposure
HAP – adjusted score	SEBT posteromedial max
Calf strength	

The purpose of the process was to predict membership of the HmAk group using non-haematological factors that may be influencing the development of HA.

Therefore the research question for this stage was:

Of the factors identified following univariate analysis as differentiating between groups, which group can form the best fitting model to predict the outcome of presenting with ankle arthropathy?

As the dependent variable was dichotomous only logistic regression may be used (Tabachnick & Fidell, 2014a). Types of multiple regression procedure are based on “what happens to the overlapping variability due to correlated IVs and who determines the order of entry of IVs into the equation” (Tabachnick & Fidell, 2014a). This has resulted in the delineation of three groups of procedure:

- Standard – all IVs are entered at once and each is assessed as if it had entered after all the others. It is evaluated by what it adds to the prediction model that is different from what the others predicted.
 - Sequential (hierarchical) – IVs entered in an order specified by the investigator which is determined a priori by theoretical considerations.
 - Statistical (stepwise) – order of entry is based solely on statistical criteria.
- Minor differences in statistics can have major influences on the equation.

For the purposes of this project, a standard regression procedure was selected.

Whilst the researcher had developed a theory as to what may have important influence on arthropathy development, the results of the Delphi determined the research direction and so personal inclinations should not take precedence over suggested factors.

Logistic regression results include explanatory variables associated with the DV and the extent of the associations. Indications of the goodness of fit to the model are presented with the analysis in terms of the Chi squared result and Nagelkerke R^2 (R^2 indicates how closely the model results are approximating the actual results). The R^2 in logistic regression is only analogous to that in multiple linear regression and does not have the same explanation for variance in the model, and so the reported result in logistic regression is the approximate variance (Tabachnick & Fidell, 2014a). Additionally, it has been suggested that this statistic is best used to compare competing models (IBM, 2016). The next section presents the results of the logistic regression process.

10.6.1 Logistic regression procedure to develop a model of prediction of haemophilia ankle group membership

The regression model was developed to determine a model of prediction for the presence of ankle HA indicated by HmAk group membership. Seven variables were put forward to the regression process and the process for identifying these variables was described in section 10.5. The seven variables selected were lifted from Table 10-9 in the order that they appear: subtalar joint inversion, ankle lunge test (ALT), human activity profile (HAP) adjusted score, calf strength, Foot and Ankle Ability Measure Sport subscale (FAAM), duration of exposure to a key sport between 3 – 16 years and Star Excursion Balance Test Posterior Max (SEBT).

After checking for that the assumption of linearity was met using the Box-Tidwell procedure, the first four items were entered into the model. Thereafter, the results were examined in terms of the pseudo- R^2 , percentage of correctly identified cases, sensitivity and specificity. It should be noted that pseudo- R^2 which is not equivalent to the R^2 used in multiple linear regression which gives a percentage of the variance, but is only approximation and has been noted as such where reported in the results. Additionally, it is recommended that it is best used as a comparative index between competing models and the results should be viewed with caution (Tabachnick & Fidell, 2014a). Table 10.10 below shows the development of the model until the point that a strong model occurred.

Table 10-10 Initial development of regression model

Model	Nagelkerke R ²	Correct classification	Sensitivity	Specificity
stj, alt, hap, cal	49.9	80.4	78.6	82.1
stj, alt, hap, faa	77.9	88.9	85.7	92.7
stj, alt, hap, dur	59.5	87.5	85.7	89.3
alt, dur, hap, sebt	58.8	88.9	85.7	89.3
alt, dur, hap, faa	82.1	88.9	85.7	92.3

Key: stj –subtalar joint inversion, alt – ankle lunge test, hap-human activity profile, cal-calf strength, faa- foot and ankle ability measure sport, dur-duration of exposure to key activity & sebt-star excursion balance test posteromedial max.

At this point, variables were substituted to ensure that the model could not be improved upon. This resulted in the identification of a model with a slightly reduced pseudo- R² but with improved sensitivity and specificity. Substitutions were made based on earlier responses in the model. This is shown in Table 10.11.

Table 10-11 Second stage of model development showing substitutions

Model	Nagelkerke R ²	Correct classification	Sensitivity	Specificity
alt, dur, faa, cal	79.2	89.7	83.3	96.4
alt, dur, faa, stj*	81.1	89.7	86.7	92.9

Key: stj –subtalar joint inversion, alt – ankle lunge test, cal-calf strength, faa- foot and ankle ability measure sport & dur-duration of exposure to key activity.
*Final model

Finally as it is recommended that a regression model should predict the DV with the fewest possible IVs where each IV predicts a substantial portion of the DV, the researcher then assessed the effects on the model of removing the non-significant variables in the model.

Table 10-12 Effects of removing items from the final model

Removed	Nagelkerke R ² -
	Initial 81.1
alt	79.7
stj	77.8
alt & stj	76.6
Key: stj –subtalar joint inversion, alt – ankle lunge test	

As removal of the non-significant items resulted in a reduction in the pseudo- R², the researcher determined that the reduction in number of items from four reduced the strength of the model and so the final model included the following variables: subtalar joint inversion, FAAM sports subscale, duration of exposure to a key sport between 3 – 16 years and ALT and of these variables FAAM sports subscale, duration of exposure to a key sport between 3 – 16 years were significant at $p = .002$ and $p = .037$ respectively. Table 10.13 presents the full results of the process.

Table 10-13 Logistic Regression Results Predicting Likelihood of Ankle Joint Disease Based on FAAM sport subscale score, Duration of Playing their Chosen Sport/Activity, Subtalar joint inversion and Ankle Lunge Test

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP (B)	
							Lower	Upper
FAAM sport	-.190	.061	9.659	1	.002	1.21*	1.07	1.36
Play duration	.568	.272	4.363	1	.037	1.77	1.04	3.01
Ankle lunge test (DF motion)	.111	.093	1.404	1	.236	.895	.746	1.08
Subtalar joint inversion	-.079	.046	2.939	1	.086	.924	.844	1.01
Constant	15.389	6.283	5.999	1	.014	4821681.30		

*presented as the inverse of the result for ease of interpretation. Items in bold are statistically significant

The logistic regression model was statistically significant, $\chi^2(4) = 54.353$, $p < .0005$. The model explained approximately 81.1% (Nagelkerke R²) of the variance in ankle joint disease group and correctly classified 89.7% of cases. Sensitivity was 86.7%, specificity was 92.9%, positive predictive value was 92.9% and negative

predictive value was 86.6%. Of the four predictor variables, two were statistically significant (as shown in Table 10.13). Increasing years of participation in their chosen sport during the period of ankle cartilage vulnerability (3 – 16 years) was associated with an increased likelihood of presenting with ankle joint disease where for each additional year the odds of having joint disease increased by 1.8 (CI 1.04 – 3.01), whereas for each unit *reduction* in the FAAM sport subscale the odds of having joint disease increased by a factor of 1.21 (1.07 – 1.36).

Odds ratios may be converted into more easily digestible percentage changes and it is considered more meaningful to utilise the change apparent with one SD of the variable when continuous data are being addressed (National Centre for Research Methods). So for one SD decrease in the FAAM sport subscale score the chances of being in the HmAk group increase by a factor of -3.74 or 97.64%. For 1SD additional play exposure time the chances of being in the HmAk group increase by a factor of 1.64, or a huge 416%. For the ALT and subtalar inversion the figures are -.76 odds and 53.22% and 1.0 odds and 170.58% respectively. The influence of exposure time can be seen to be greatest in the model.

A consideration with regression analysis is the ratio of cases to IVs which has to be substantial or the solution will be both perfect and meaningless. A simple rule of thumb is: N (total study cohort) $\geq 50 + 8m$ where m is the number of IVs (Tabachnick & Fidell, 2014b). In this case by selecting a model with the fewest possible IVs explaining a large part of the variation in group membership:

$$N \geq 50 + 8*4 = 82.$$

Therefore in this case, the solution can be said to have meaning from a sample size perspective. The between group means and standard deviations are presented below for the two significant factors (Figures 10.7 and 10.8).

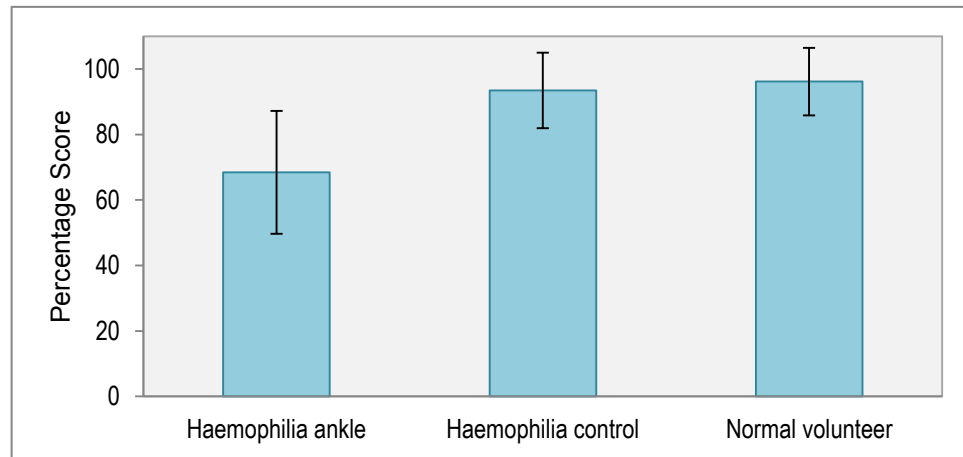


Figure 10-7 Between-group comparison for the FAAM sport subscale

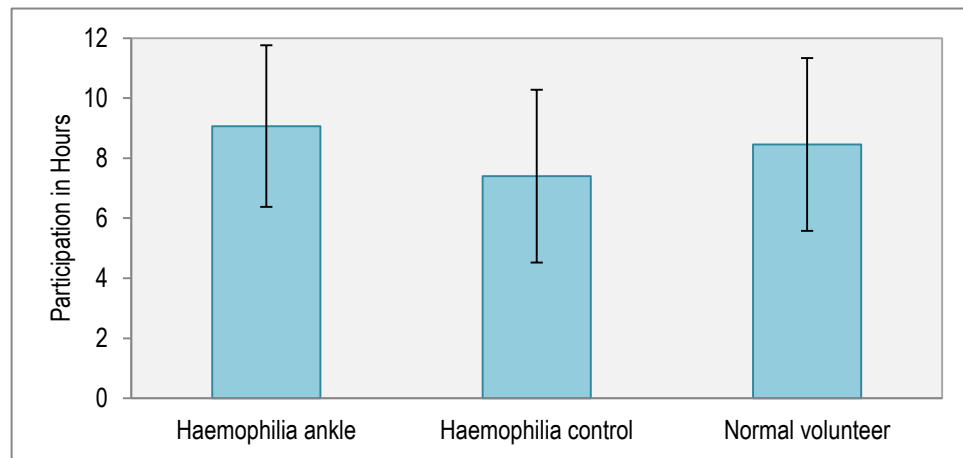


Figure 10-8 Between-group comparison for duration of playing key activity

10.6.2 Determining a cut-off point for the FAAM sport subscale that reflected haemophilia ankle group membership

The FAAM sport subscale demonstrated high significance during all analyses procedures. As this is a self-perceived functional score encompassing many clinical domains the researcher considered it worthwhile to investigate whether any of the measured factors were explanatory for this variable as it is in turn explanatory for ankle group membership. For this to occur, it was necessary to determine a cut off point for the FAAM sport subscale to identify membership of the ankle joint arthropathy group. A Mann-Whitney test confirmed that there was a significant difference between the FAAM sports subscale scores for those in the haemophilia groups with and without ankle joint disease, $U=783$, $z=4.998$, $p=.0005$. Analysis of the ROC curve and analysis of point co-ordinates indicates that 90% is the best cut off point giving a sensitivity of 90% (C.I. 73.47% – 97.89%) and a specificity of 86.67% (C.I. 69.28% - 96.24%), see Figure 10.9.

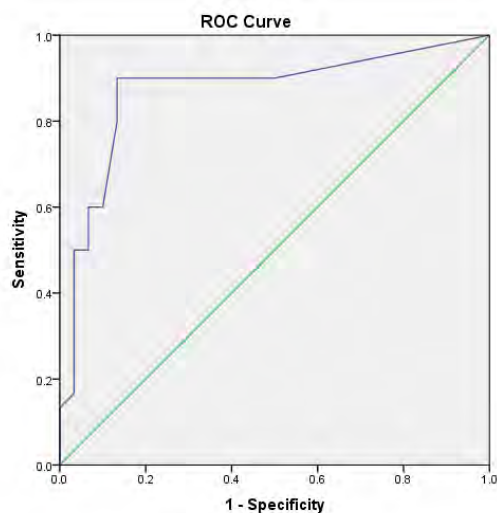


Figure 10-9 ROC curve for Foot & Ankle Ability Measure (sports subscale) demonstrating a 90% cut-off for 90% sensitivity.

Analysis of AUC of the ROC graph gave 0.87 indicating a good performance.

Therefore the FAAM scores were dichotomised at ankle joint disease present at scores less than 90% and absent in scores of 90% and greater.

The next section presents the development of a regression model able to predict the presence of a FAAM sports subscale score of equal to or less than 90% in order to identify potential factors indirectly influencing the development of ankle HA.

10.6.3 Logistic regression procedure to develop a model of prediction of FAAM sport - ankle group membership

The researcher considered that potentially physical measures and aspects pertaining to participation in the key sport/activity might impact on this score.

Therefore an additional logistic regression was performed using the original group of 14 significant variables as a starting point again. The process determined that the effects of calf strength, SEBT posteromedial maximum reach, range of ankle joint complex dorsiflexion and overall fitness on the likelihood that participants belonged to the FAAM less than 90% group. Table 10.14 presents the results of the procedure.

Table 10-14 Logistic regression results predicting likelihood of achieving a FAAM sport subscale score indicating likelihood of ankle joint disease based on Human Activities Profile adjusted score, Ankle Lunge Test , calf strength and SEBT posteromedial maximum

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP (B)	
							Lower	Upper
HAP adjusted	-.151	.045	11.30	1	.001	.866	.787	.939
Ankle lunge test (DF motion)	-.188	.074	6.389	1	.011	.829	.717	.959
Calf strength	.067	.085	.615	1	.433	1.0169	.905	1.203
SEBT posteromedial Max	-.029	.035	.618	1	.432	1.028	.960	1.101
Constant	11.492	4.181	7.555	1	.006	97895.205		

Items in bold are statistically significant.

The logistic regression model was statistically significant, $\chi^2(4) = 35.430$, $p < .0005$. The model explained approximately 54.5% (Nagelkerke R^2) of the variance in FAAM sport subscale scores and correctly classified 80.4% of cases. Sensitivity was 81.5%, specificity was 79.3%, positive predictive value was 82.1% and negative predictive value was 78.6%. Of the four of the predictor variables, two were statistically significant. Results indicated that for each unit reduction HAP adjusted score and Ankle Joint Complex dorsiflexion there was an increase in odds of having a FAAM sport subscale score correlating with ankle joint disease (HAP .866 (C.I. .79 – .94) and ALT .829 (C.I. .717 – .959)).

10.7 Exploration of Activity and Exercise Questionnaire Data

The data collection from the exploratory activity and exercise questionnaire described in Chapter 8 had a twofold purpose: firstly, for the collection of information pertaining to historical occupation, exercise and injury patterns and secondly to inform the format of a future qualitative study concerning attitudes to

activity and exercise participation. These interim data analyses present the first data group only in relation to its potential to impact on arthropathy development. Descriptive education and occupation data derived from this questionnaire were presented in section 10.3 above. The following data represents historical exercise and injury patterns.

10.7.1 Historical activity data

Tables 10.15 and 10.16 present a full list of activities/exercise for the full cohort including ankle risk coding described below and in Appendix 16. Similar activities were grouped together such as martial arts disciplines that involved kicking. An inspection of these data indicates that PWH with ankle joint disease appear to be largely unlimited in terms of types of activities undertaken in comparison with their peers. A wide variety of activities was reported ranging from alpine skiing to yoga with such diverse things as ballet, orienteering and martial arts in between. The HmAk group reported 32 activities, the HmC group 38 and NV group 36.

Table 10-15 Low ankle injury risk activities divided by group

Activities	HmAk	HmC	NV	Count
Low risk	63	76	57	197
Badminton	1	1	1	3
Baseball	1	1		2
BMX	1			1
Boxing			1	1
Canoeing		1		1
Cycling	8	9	7	24
Dog Walking	1	1		2
Domestic Activity			1	1
Golf	4	1	1	6
Gym Various/Personal Fitness	4	5	3	12
Hiking		6	4	10
Ice Hockey			1	1
Jogging/running	5	5	7	17
Orienteering/Cadet Training/Cross Country Running	1	1		2
Outdoor/Scouting Activities		2	2	4
Paper Round		2		3
Pilates			1	1
Pool/Billiards/Snooker	1			1
Riding		1		1
Rowing		1	2	3
Surfing		1		1
Swimming	15	17	6	38
Table Tennis	3	4	1	8
Walking	16	16	17	49
Weight Training	1			1
Yoga			1	1

HmAk = Haemophilia Ankle group, HmC = Haemophilia Control group, NV = Normal Volunteers

Table 10-16 Moderate and high ankle injury risk activities divided by group

Activities	HmAk	HmC	NV	Count
Moderate risk	33	34	34	103
Alpine Skiing	1	1		2
Athletics/Track & Field	4	2	1	6
Cricket	5	4	2	11
Dance			2	2
Gymnastics			1	1
Ice Skating	1			1
Judo			1	1
PE Classes	10	9	16	35
Physical Theatre			2	2
Playground Games	4	5	3	12
Rollerblading		1		1
Snowboarding		1		1
Squash	4	3	2	9
Touch rugby		1		1
High risk	34	29	20	91
Ballet			1	1
Basketball	8	4	1	14
Football	18	20	14	52
Gaelic Football			1	1
Hockey		1		1
Hurling	1			1
Martial Arts (kicking disciplines)	1		2	3
Rugby	3	2	4	9
Skateboarding/Longboarding	2			2
Tennis	7	8	2	18
Triathlon		1		1
Volleyball		1	1	3

HmAk = Haemophilia Ankle group, HmC = Haemophilia Control group, NV = Normal Volunteers

Participants described 57 activity/exercise choices in total, some were only played for a short period of time or were taken up as an adult and so, as the researcher had surmised that activity during childhood might be important, a key childhood activity was identified for each participant. The key sport or activity was selected from the period of ankle articular cartilage development when at its most vulnerable developmentally that is, 3 – 16 years. For this activity, the age that they began participating and the duration of exposure in years were also identified for use in

regression analyses. The activity was selected based on duration of participation in years, highest level of competition and the likelihood of injury to the ankle joint. For this latter domain the researcher compiled an ankle risk table based on injury epidemiology available in the literature and used expert opinion where this was not (see Appendix 17). Activities and sports were ranked as low, moderate or high risk based on ankle injuries per exposure metric. Of the 57 activities/sports reported across the groups, 12 were classified as high risk to the ankle joint. These were: football (including 5-a-side), basketball, hockey, hurling, martial arts (kicking disciplines), skateboarding, rugby, tennis, triathlon, volleyball, Gaelic football and ballet. Figure 10.10 presents the key activity data sorted by group membership and Figure 10.11 presents the activities sorted by risk of injury to the ankle and reported injuries.

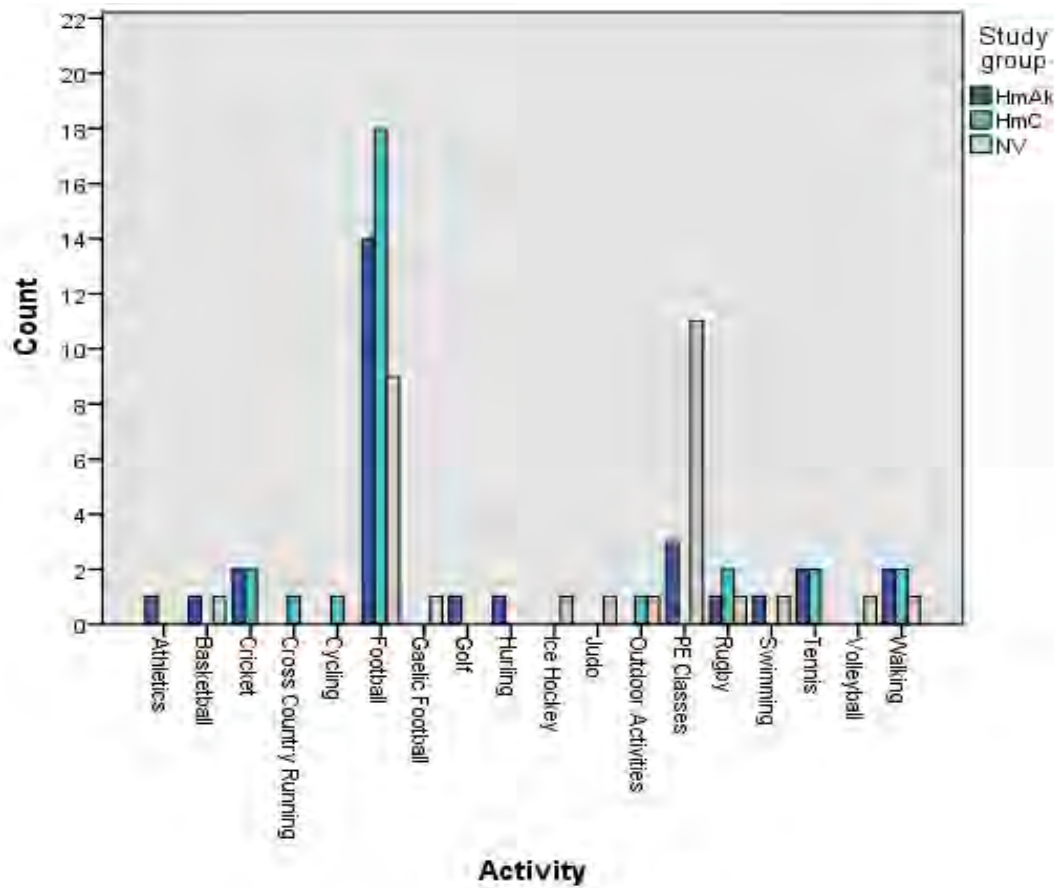


Figure 10-10 Identified key activity presented by group membership.

Groups: HmAk = Haemophilia Ankle, HmC = Haemophilia Control, NV = Normal Volunteers.

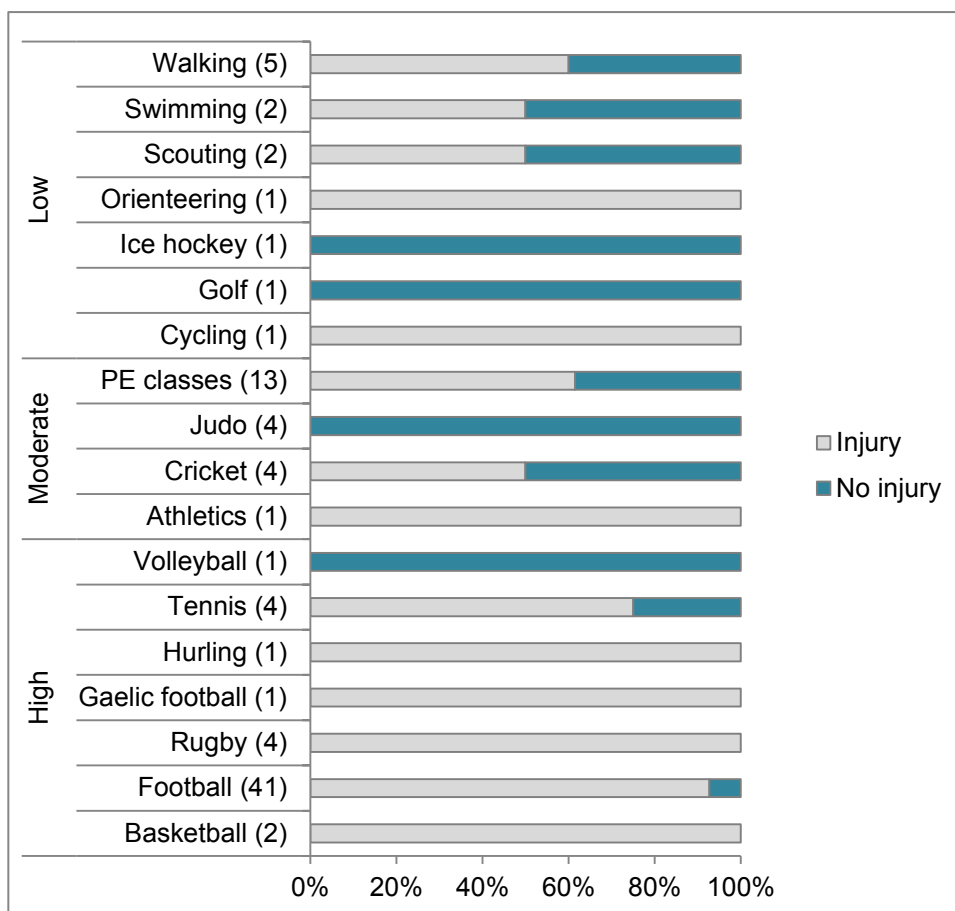


Figure 10-11 Key activities and sports divided into ankle injury risk categories with the percentage of reported injuries during participation. Number of participants in parentheses.

Analysis of key activity data showed that more people in the haemophilia groups participated in riskier activities (see Figure 10.12). Furthermore, more injuries occurred in the higher risk activities in the HmAk group compared to either of the other groups (see Table 10.17 below). Although the difference in injury rate between the HmAk group and the others is approximately 20% this is not statistically different (Chi square X^2 (2), 5.077, $p=.079$).

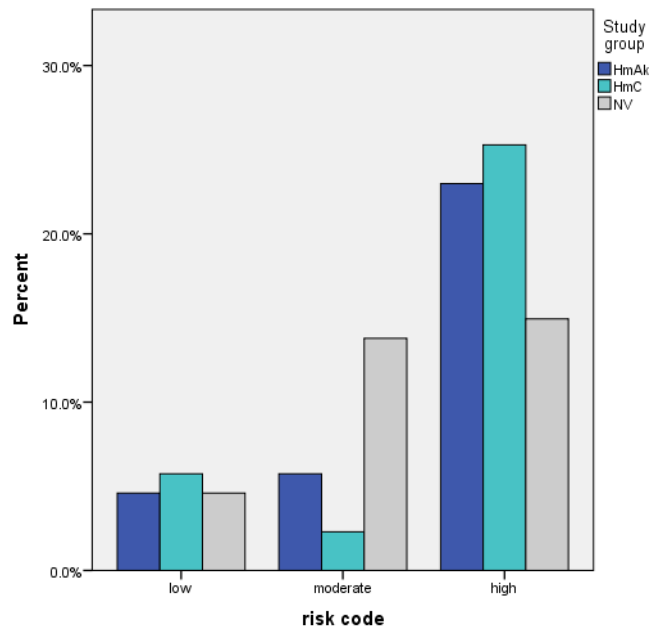


Figure 10-12 Group participation in sports rated by ankle injury risk.

HmAk = haemophilia ankle, HmC = haemophilia control and NV = normal volunteers.

Football was the most commonly played high risk key sport which is reflective of the sport's popularity; it also has the highest injury rate (not considering injury rates in activities with only one reported participant). It is interesting to note that a higher percentage of participants in the HmC group reported playing football than in the HmAk group and also reported a high rate of injury. However this does not seem to have affected their ankle joint health indicating that the sport itself or the sport alone may not be influential in arthropathy development. The reported football injury rate (see Table 10.17) indicated that all participants in the HmAk group and most of the HmC group sustained injuries. Between 16 – 23% difference exists between the NV group and the haemophilia groups indicating undetermined factors that increase injury risk in haemophilia in general.

Table 10-17 Activity risk data. All figures are percentages.

	Haemophilia Ankle	Haemophilia Control	Normal Volunteer
High risk activity participation	50	53.3	33.3
Injuries in high risk activity	87.5	60	66.6
Football participation	46.67	63.3	30
Injuries in football	100	94.4	77.8

An exploration of the reasons given for injuries sustained during all activities in all groups indicated that the 47.2% participants believed their injuries were accidental in nature which would suggest a lack of preventability however, 44.3% of others suggest injury reasons with the potential for prevention. Table 10.18 displays injury reason separated by theme: accidental, preventable, haemophilia and miscellaneous. (NB some participants gave multiple reasons for injuries; these were divided into the separate themes.) Collisions, “over doing it” and training errors were the most frequently cited reasons. Because some participants listed multiple reasons for injuries for a given activity it is not possible to ascertain if members of the HmAk group were suffering more of a particular injury type. Additionally, the type of resultant injuries was not ascertained although some participants gave “sprain” or “strain” as an injury reason.

Table 10-18 Reasons given for sustaining injuries across groups and all activities

Accidental	150	Preventable	141
Accident	26	Careless	5
Ankle sprain	13	Continuous play	1
Collision	68	Insufficient warm up	11
Collision - equipment	7	Landing	2
Collision - person	4	Over did it	69
Falling	6	Repetitive strain	1
Impact	7	Rushing	1
Over did it	5	Technique error	6
Slip/twist	4	Training error	45
Sprain/strain	10		
Haemophilia	18	Miscellaneous	9
Ankle damage	2	All sorts of reasons	3
Bleeding	5	Bad surface	1
Bleeds not settling	4	Careless	1
Not resting enough	4	Seizure	1
Training error/ bleed	2	Top heavy weight bearing	2
My blood doesn't clot	1	Various	1

Participants were asked to recall if they felt that they had been as active as their peers at five, ten and fifteen years of age and also whether they had played the same games overall. Whilst the types and duration of participation of activities described above indicated that PWH were partaking at least as much as those in the NV group their self-perception indicated otherwise. Figure 10.13 shows the comparison across age groups. It can be seen that as members of the HmAk group aged they perceived that they were doing progressively less exercise than their peers (reported by 26.67% age 5 to 40% age 15) whereas for the HmC group, a reduction in activity appeared to occur later. Even at age 5, the HmAk group perceived that they were doing less than their peers (reported by: HmAk group 26.67%; HmC group 13.79% & NV group 3.33%). At age 5 the researcher

considers that limitations are less likely to be self – imposed and so parents/carers and indeed clinicians must be looked to for the reasons for this.

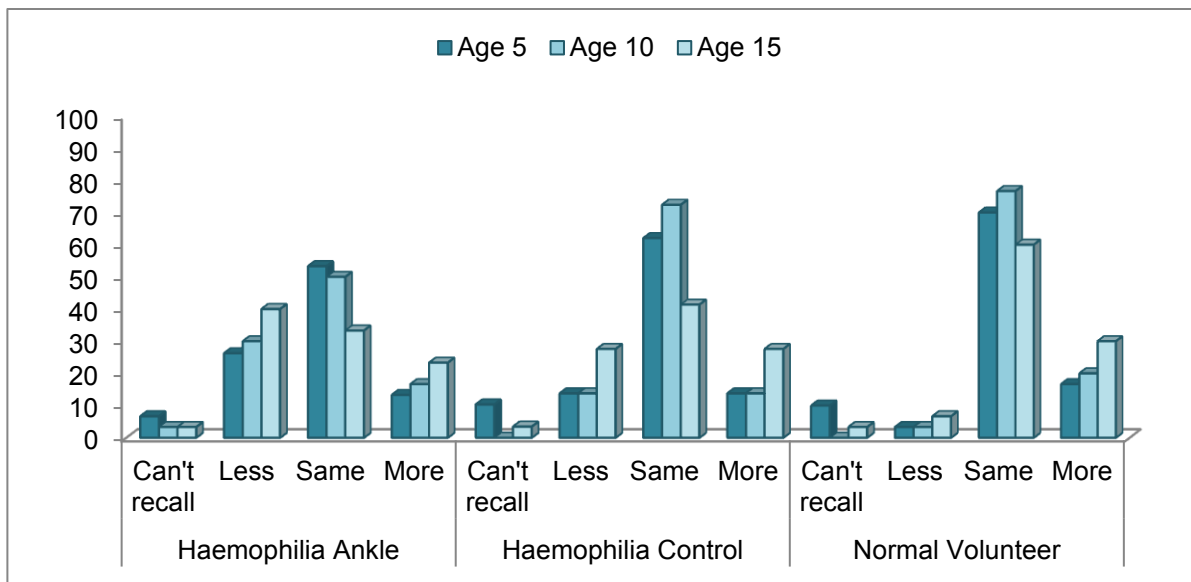


Figure 10-13 Comparison of recalled activity levels at ages 5, 10 and 15.

Additionally between 24% - 30% of PWH do not feel that they took part in the same amount of activities as their peers overall as children. This is shown in Figure 10.14.

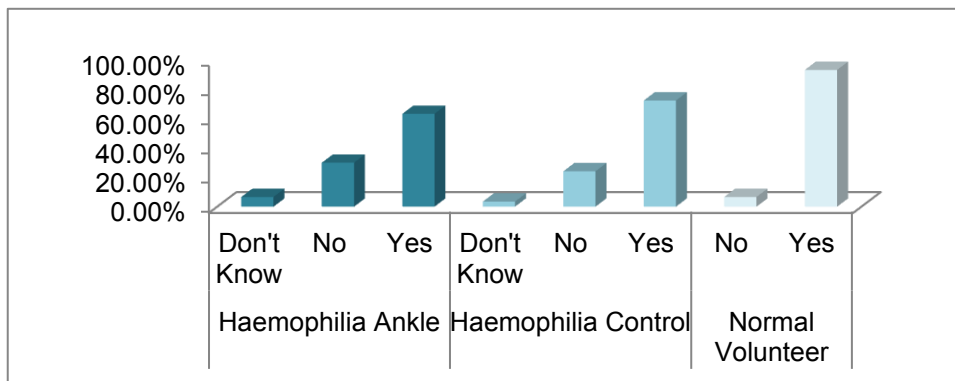


Figure 10-14 Comparing the perception of amount of activity participation as children.

Response to the question: Overall did you run around the same as your peers?

Historical exercise data gave an over-arching impression that members of the haemophilia groups have a similar exercise and activity profiles compared to their peers however injury rates appear to be higher. Their participation in more

activities deemed by the researcher to be risky to the ankle is an interesting finding and worthy of further investigation as the current data set precludes speculation on the underlying reasons for this.

10.8 Summary and Key Findings

Following between group analysis 14 items were found to be different across the groups. Of these, the FAAM, CAIT, HAP, ankle lunge test, anterior drawer and single leg squat test were able to discriminate the HmAk group from the others however, the researcher considered that the latter two were highly likely to represent changes and adaptations secondary to the presence of HA in the group. Subtalar group inversion and eversion, along with calf strength, were statistically significant between the haemophilia groups and the normal volunteers which may indicate previously unreported changes unique to haemophilia.

The regression model developed to identify membership of the HmAk group and comprising the FAAM sport subscale, duration of play, ankle lunge test and subtalar inversion, could successfully identify 89.7% of cases with 86.7% sensitivity and 92.9% specificity. As the FAAM sports subscale, a tool whose outcome can be influenced by many physical factors, had been so clearly discriminatory throughout the analysis process, a further regression model was developed utilising a cut-off of 90% (which provided 90% sensitivity) in order to see if any of the other investigated factors contributed to this group membership. The model utilising HAP adjusted score, ankle lunge test, calf strength and SEBT posteromedial max score approximately explained 54.5% of the variance in FAAM sport subscale scores and correctly classified 80.4% of cases. The researcher considers this interesting from

two perspectives. Firstly, the concept of arthropathy development being multifactorial is reinforced by the FAAM sports subscale score being predictive of HmAk group membership and that other physical factors are in turn affecting FAAM outcome. Secondly, the 54.5% variance in FAAM sports subscale scores represented by the regression model suggests that there are other influences waiting to be identified.

The research journey from 280 original Delphi suggestions to a regression model comprising of just four factors is complex and could be considered a radical reduction in considered factors and so Figure 10.15 present this journey to further explicate the researcher's reasoning processes.

At this point it should be re-iterated that regression analysis does not reveal causality amongst tested variables merely relationships. Strong relationships may be related to many causes including currently untested influences (Tabachnick & Fidell, 2014b). The next chapter will discuss this implication and further develop rationales to explain these results and findings.

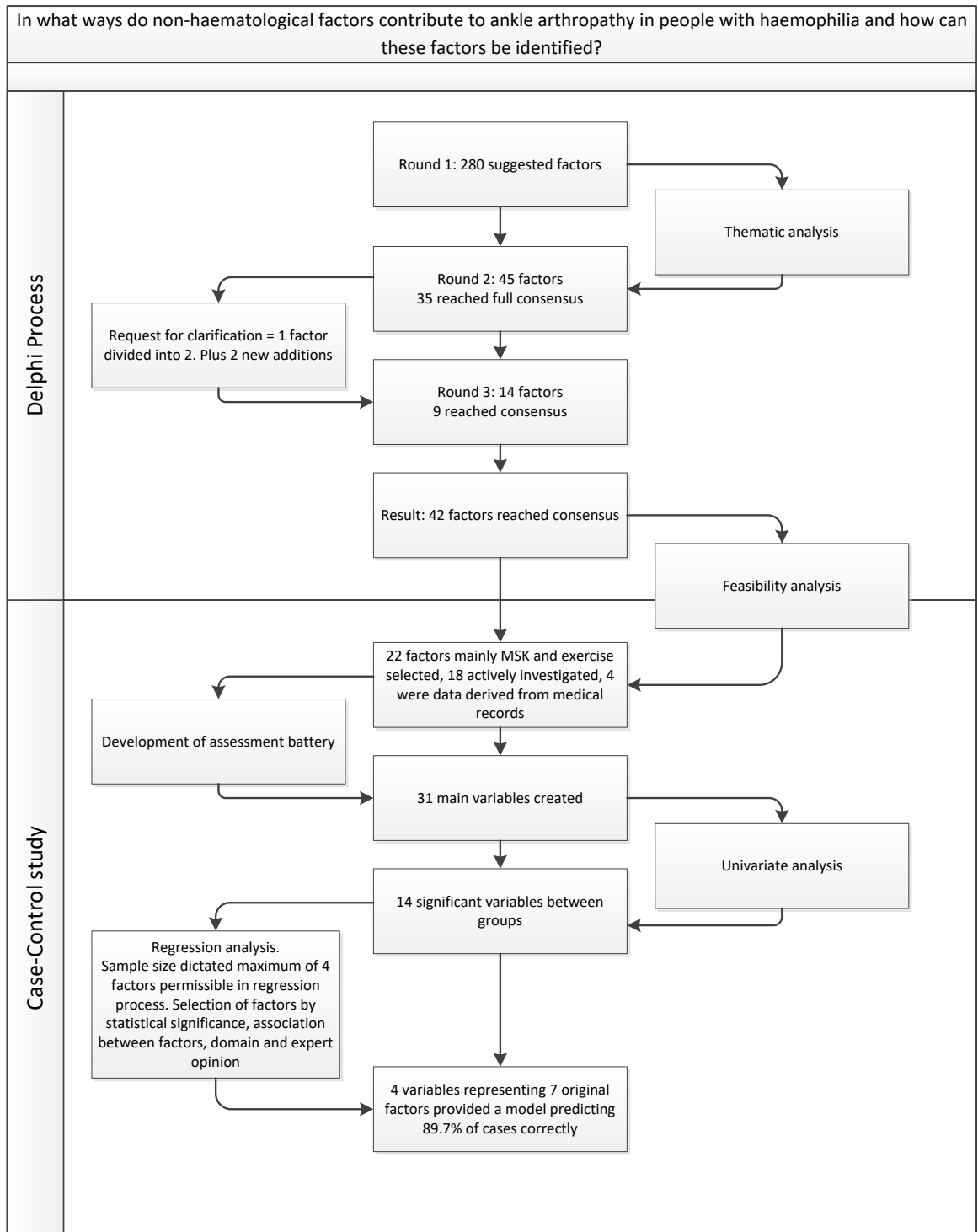


Figure 10-15 Overall Management of Factors Investigated in the Research Programme from Delphi Generation to Regression Analysis

Chapter 11 Main Study: Evaluation of the Effect of MSK and Exercise Factors on the Development of Joint Disease in Haemophilia - Discussion

11.1 Introduction

Years of effective prophylactic factor replacement therapy has failed to eliminate haemophilic arthropathy (HA). To the researcher, development of HA is a complicated problem that requires an open-minded and flexible approach to investigation. The majority of published literature on pathoetiology of the condition focusses on biochemical pathways but the Delphi study reported in this thesis has shown that expert clinicians in the field understand the condition initiation to be far more complex. Therefore a research programme was developed with the overall aim of investigating the multifactorial nature of the development of joint disease in haemophilia using the normally robust ankle joint as the focus.

The over-arching research question for this study, "*In what ways do non-haematological factors contribute to ankle arthropathy in people with haemophilia and how can these factors be identified?*" has been phrased in a such a way as to recognise the exploration which the research problem requires and also to preclude restriction of the researcher's view by focussing the study direction a priori. This led to a three-phase programme: an exploratory-direction finding Delphi study; preliminary developmental study design work and finally a case-control study. The former two phases have been discussed at length as part of their respective chapter and this discussion chapter will focus mainly on the case-control study.

From the original 42 Delphi factors that reached consensus, 17 factors, focussed on MSK intrinsic factors and exercise, were actively investigated in a case-control correlational study. Three research subsidiary questions were developed from the overarching question for the case-control study:

- Q1. Are selected clinical instruments suitable for use with PWH?
- Q2. What instruments with high clinical utility are able to discriminate between those PWH with and without haemophilic ankle arthropathy?
- Q3. To what degree if any, are investigated factors related to the presence of haemophilic arthropathy?

This discussion is structured to explore these questions in the first instance. It then discusses the exploratory activity data and draws on these discussions to explore and/or explain the overarching research question. Finally matters arising from the study design and implementation, including a review of study limitations, are presented.

11.2 Q1 Are Selected Clinical Instruments Suitable For Use With PWH?

The case-control study has produced a number of interesting and significant results and findings which support the researcher's premise that the pathoaetiology of HA is multifactorial in nature. A number of factors were identified that can distinguish between PWH with ankle HA and PWH-controls and normal volunteers (discussed under Q2). However it is first necessary to discuss whether the chosen clinical instruments were fit-for-purpose.

11.2.1 Safety

This thesis reports the results of 90 participants undergoing the full study protocol and there have been no reports of adverse events or latent bleeds indicating that the protocol is safe for PWH. The Timed Single Leg Stance (TSLs) test was noted to be fatiguing or uncomfortable by several participants. However, when given the option, none opted out of completing the test. Only one participant opted out of a test, the Tecumseh step test, which the local PI felt might be due to embarrassment over lack of fitness.

11.2.2 Sensitivity of tests to identify ankle arthropathy

Tests selected for inclusion in the study demonstrated discriminant validity in other existing conditions. For instance the Star Excursion Balance Test with chronic ankle instability (CAI) (Olmsted, et al., 2002), and the FAAM has utility in a number of lower limb conditions (Martin, et al., 2005)). Alternatively they were well used in the literature with available normative data for comparison (e.g. Tecumseh step test (Montoye, et al., 1969) and Foot Posture Index (Redmond, et al., 2008)). The discriminant ability of the tests with regards to HA is discussed in the next section however the researcher thought it pertinent to discuss certain measurement tools whose findings, significant or insignificant, are thought-provoking with regards to suitability for use to identify the presence of HA at the ankle. The overall performance of the study protocol with regards to suitability for PWH is discussed at the end of the section.

It was interesting to note that several tests did not provide expected results in terms of statistical significance and/or direction of differences. Notably the SEBT, which was selected as a multiple function test for dynamic balance, lower limb

strength, ankle dorsiflexion challenge and general lower quarter co-ordination thereby investigating multiple factors, appeared to the researcher on observation to particularly challenge the HmAk group in the anterior reach direction. This would be in keeping with reduced dorsiflexion range of movement and anterior loading of the joint that this direction requires. However, the result indicated no statistical differences between groups (SEBT anterior reach mean differences HmAk to HmC 3.41cm and HmAk to NV 2.77cm, $p = .38$). In the other reach directions there were more sizeable mean differences of 4.4cm for the maximum posteromedial reach and 4.13cm for the maximum posterior reach directions between the HmAk (greater reach) and HmC groups that were still not significant. What is of great interest is that the HmAk group performed consistently better than the HmC group in all directions. The HmAk group also performed better than the NV group in the anterior reach direction, but in the others the NV group was better. This is unexpected as it might be surmised that the HmAk group would perform poorly compared to the others due to existing arthropathy. This may reflect a clinically important result without statistical support, as a 4cm difference has been shown to be significant in a CAI population (Olmsted, et al., 2002) and the between group differences here are on a par but are of “reverse polarity” with the HmAk group achieving greater reach distances. The only study in the haemophilia literature to examine clinical balance tests recruited a cohort of PWH with mixed joint health status (i.e. 4 participants with recorded joint replacements etcetera) versus healthy controls. It used a barrage of tests but did not include the SEBT. The authors reported that the haemophilia cohort had a “moderate balance impairment” (Fearn, et al., 2010) which does not concur with current results for dynamic balance.

However, the studies are not directly comparable due to inclusion criteria and methods used.

SEBT has been shown previously to be able to detect differences in those with CAI (Hubbard, et al., 2007) and anterior cruciate ligament deficiency of the knee (Munro & Herrington, 2010) where the affected side had reduced reach distances. It is contrary to expectations therefore in this study that the affected side in PWH showed consistently greater reach distances. The researcher proposes that the duration of symptoms in PWH may have led to the development of very good compensatory mechanisms in terms of proprioception where visual and muscular elements may have adapted to offset losses due to alteration in joint mechanoreceptors. Moreover, the better test scores by the HmAk group may be a reflection of the insidious onset of the condition. As the condition initiates in childhood at a time of high physical activity, these adaptations have time to develop well. There is also the potential for a positional contribution whereby both posterior and posteromedial reach directions require a forward trunk lean lowering maintaining the centre of gravity within the base of support with a closed pack talocrural joint position which might unconsciously be perceived as more stable, without going to the potential discomfort of end-range required by the anterior reach. A search of the literature failed to find any examples of the SEBT in use with non-traumatic long term conditions. This may therefore be the first study to provide results with an insidious onset chronic condition. The utility of this tool for detecting deficits thought to be associated with HA at the ankle is unclear as these hypothesised deficits were not apparent. However, it might well prove capable of identifying PWH with developing joint disease if their performance begins to outstrip their peers. Further investigation is needed into this phenomenon.

Conversely, two other tests although significant were not suitable as they could be perceived to be reflecting the HA disease process, even in the highly functional group recruited, rather than potentially underlying influencing factor differences between groups. The first of these, the Single Leg Squat Test (SLSq, $p < .0005$), was selected as a measure of pelvic control reflecting part of the “altered biomechanics of the lower limb” factor. The test requires a squatting manoeuvre on one leg as if stepping down from a small step and is intended to show any compensatory mechanisms in the leg, pelvis and trunk where the performance deviates from ideal (Crossley, et al., 2011). It became rapidly apparent in the HmAk group that many of the observed compensations were in fact the result of any restricted ankle dorsiflexion present rather than pelvic control issues. Therefore this test was considered to have not produced valid results and was unsuitable for use in PWH with ankle HA.

The second test was the Anterior Drawer Test which examines the integrity of the ankle lateral ligament complex and the anterior talofibular ligament in particular (Croy, et al., 2013) and represented the “specific foot and ankle biomechanics” factor. This test again differentiated between groups ($p = .001$) and separated the HmAk group from the others. However a review of the raw data indicated that the difference lay in the number of hypomobile recordings for this group (43.3% compared to 16.6% HmC and 6.67% NV), indicating that ligamentous laxity was not assessed in the HmAk group due to the restriction in joint glide. Equating that with the underlying Delphi factors, it has been proposed that specific lateral ligament laxity is not a risk factor for ankle sprains (“history of ankle injury” was a factor) as the supination moment during a spraining manoeuvre occurs in advance of reaching lateral ligament tension, and so any observed laxity could be an effect

rather than a cause or recurrent sprains (Fuller, 1999), however a component of primary hypermobility is reduced proprioception which is partly determined by neural receptors in ligaments. So while, this test has not been found to be useful in this cohort, the researcher cannot rule out ankle lateral ligamentous laxity as an influencing factor for HA development.

The choice of some of the tests was predicated on their being the “gold standard” in the current literature such as the Beighton score for joint hypermobility. It was selected as the classic test for the presence of generalised joint hypermobility and that whilst the literature acknowledges that it may miss some important joints (Grahame, 2003), it is still in everyday use. The joints included in the score (knees, elbows, 5th metacarpophlangeal, whole spine and thumb complex) partly match those commonly targeted in haemophilic arthropathy: elbows and knees. This means that the presence of low grade, even pre-clinical disease could erase signs of hypermobility and skew the resultant score. Moreover, the inclusion of the elbow joint within the score is puzzling as extension of this joint is limited by bone-to-bone contact rather than any ligamentous restraint. Notwithstanding this, the test was not significant ($p = .279$) despite there being nearly twice as many people in the HmAk group (9 participants) as the HmC group (5 participants) with a score of greater than 4 out of 9 indicating the presence of hypermobility (Connelly et al., 2015). The researcher did observe across the groups that the most commonly positive finding was hypermobility of the 5th metacarpophalangeal joint, present in 35.6% of the cohort. This phenomenon has also been noted in a UK-based paediatric epidemiology study where 29% of mean age 13.8 boys had hypermobile fingers (Clinch, et al., 2011). This finding perhaps suggests that identifying joints more appropriate to PWH that is, not the knee and elbow, may be a direction of

travel. Additionally the researcher had included alternate ways of identifying hypermobility with the intention of selecting the most useful to PWH based on results. Neither the Brighton criteria (which includes the Beighton score as a major criterion) nor the 5-point hypermobility questionnaire were statistically significant and so may not be of further use delineating this issue.

Overall, the researcher considers that the selected protocol was suitable as several tests, representing different domains, were significantly different between groups as will be discussed in the next section and so the protocol was largely fit for purpose. Adding to protocol suitability was the ease of application with no individual investigators reporting difficulties with the measures or submitting persistent outlying results that may be indicative of measurement error. The next section will discuss tests that did successfully discriminate between groups.

11.3 Q2 What Instruments, With High Clinical Utility, Are Able To Discriminate Between Those PWH With And Without Early Ankle Haemophilic Arthropathy?

Seventeen measurement tools were used in this study (please refer to Table 6.2) of which six were able to distinguish the HmAk group members from the other groups. These results are shown in Table 11.1 for ease of referral, and will be discussed in turn except for the Anterior Drawer and SLSq tests which were discussed in the previous section.

Table 11-1 Measurement tools able to discriminate between groups. Drawn from Tables 10.4 to 10.8

Haemophilia Ankle Group versus Haemophilia Control & Normal Volunteers			
Measure	Between groups result	Pairwise comparison	
		HmC	NV
Ankle lunge test	.002	.004	.0005
Cumberland ankle instability tool	.0005	.0005	.0005
HAP Adjusted	.0005	.001	.001
FAAM ADL subscale	.0005	.0005	.0005
FAAM ADL functional score	.0005	.0005	.0005
FAAM sport subscale	.0005	.0005	.0005
FAAM sport functional score	.0005	.0005	.0005
FAAM global function rating	.0005	.01	.0005
Anterior drawer test*			
Single leg squat test*			
HAP = Human Activities Profile, FAAM = Foot & Ankle Ability Measure. *These test results have low clinical value due to underlying suitability issues described in the previous section.			

11.3.1 Ankle lunge test

This test measures the combined DF motion available at the ankle joint complex as part of the “specific foot and ankle biomechanics” factor, and ably detected that the HmAk group mean range was less than the others (HmAk 7.23cm +/- 6.63, HmC 12.70cm +/- 5.86 and NV 14.19cm +/- 2.98). It could be argued that the reduced range is a manifestation of the disease process and so the test is not useful for discriminating early joint disease. This cause and effect scenario has been discussed in the literature. A reduction in DF has been suggested as a risk factor for increased risk of ankle sprain (de Noronha, et al., 2006), which the researcher has argued may be part of the pathoetiological picture, but a reduction in DF was not found in a prospective study of 233 physical education students investigating gait biomechanics in relation to potential to sustain LAS (Willems, et al., 2005)

where the authors concluded that any DF reduction noted in other studies was effect rather than cause. They went on to point out that the upshot of a persistent reduction in DF may be a more PF position of the foot at touch down in gait which has been postulated to contribute to likelihood of LAS (Spaulding, Livingston, & Hartsell, 2003). In haemophilia gait literature a reduction in range of DF in gait was not noted in a study comparing 14 boys with ankle arthropathy with healthy peers (Stephensen, Drechsler, et al., 2009). However, actual range of DF was not measured rather DF/PF motion was recorded through the gait cycle. Therefore it is not known if an actual reduction in range was present, the magnitude of loss being not enough to impact on the gait cycle.

A further consideration is that the result was possibly skewed by the presence of boys undergoing a growth spurt in the HmAk group as reduced DF secondary to triceps surae muscle group tightness during growth spurts is known (Tabrizi, et al., 2000). A review of the raw data do not indicate a persistent reduction in DF across participants across the appropriate age range and so the researcher cannot conclude that active growing played a part in the result.

So the researcher considers that the reduced DF present may be the result of early inciting events such as LAS and that prospective monitoring an individual's DF range may help identify those where subtle deficiencies are showing and are thereby at increased risk of future ankle trauma at the very least. Normative ranges have been published but it would be difficult to compare locally unless the same methods were being used; intra-individual measures may be the most apposite way, consistently using the same method across time. The HJHS does include a goniometric non-weight-bearing measure of DF but this method is considered

unreliable (Gatt & Chockalingan, 2011). Therefore the researcher draws the following inferences from these results: the ankle lunge test is able to identify those in the HmAk group and the reduced DF present may be useful as an indirect marker of altered gait, joint loading or early joint damage.

11.3.2 Cumberland ankle instability tool (CAIT)

This tool, included in recognition of the “history of injury” and “proprioceptive deficits” factors, was equally able to differentiate the HmAk from both of the other groups ($p = .0005$); this result is based on using the mean score. A cut-off point of less than or equal to 27.5 has been identified in the literature as indicative of the presence of chronic ankle instability following lateral ankle sprain (Hiller, et al., 2006) but it would appear a lower score is indicative of HmAk group membership with a score of 25.5 yielding 87% sensitivity and 77% specificity. As it is unlikely that this tool would be used in isolation but rather as part of a full medical and therapeutic assessment, the researcher considers that detecting positive cases appears more important than correctly identifying negative cases and so sensitivity and specificity levels are, although not good, acceptable. This would not be the case if the tool were to be used in isolation where 95% sensitivity would be ideal.

This is a quick tool to complete with a high degree of clinical utility. Utilising subjective instability as a screening tool in PWH has not previously been suggested in the literature. The clinical Haemophilia Joint Health Score (HJHS) does not contain items that might reflect the presence of ankle instability but rather global gait function (Hilliard, et al., 2006). A perception of instability could conceivably be an early indicator of pre-clinical joint issues. Clinically PWH have reported a of sense instability but sometimes haven't actively perceived it until it is

gone, for instance with the provision of an orthotic or a more stable shoe. A perception of instability has also been reflected in the chronic ankle instability literature where self-reported questionnaires were found to be more accurate than sensorimotor outcome measures at identifying those with persistent ankle problems compared with those with a history of sprain but no ongoing issues (Wikstrom, et al., 2012). Detecting instability is important because of the potential of increasing shear stresses at the articular surfaces as it is known that high shear stresses are detrimental to AC health (Carter, et al., 2004). Tochigi et al. (2008) put forward the proposal that some instabilities may be undetectable by conventional techniques, laboratory or clinical, leading to an accumulation of minor insult to articular cartilage occurring over a period of years and eventually leading to degradation. This idea may be reflected in the insidious development of HA. A perception of instability at the ankle might exert a subconscious or subclinical impact on an individual, making them reticent about physical activity which may in turn impact on their overall fitness an aspect of which, aerobic capacity – reflecting the “reduced general fitness” factor, was investigated using the next tool.

11.3.3 Human Activity Profile (HAP)

This survey gives an indication of aerobic fitness and differentiated between those in HmAk and those in the other groups using the HAP adjusted score ($p = .001$). The other possible outcome, the maximum score, differentiated the HmC group from the others and therefore lacks value for the study purpose. There was an 18 percentage point difference between the HmAk group and the NV that suggests that members of the HmAk have less aerobic fitness than the other groups. There was also a 9.7 percentage point difference between the NV and the HmC which might indicate an issue with overall aerobic fitness in haemophilia populations. The

evidence surrounding fitness in haemophilia is mixed with some studies finding equivalent aerobic fitness to healthy peers mainly in paediatric cohorts (Douma-Van Riet, et al., 2009) whereas others have found reduced fitness (Koch et al., 1984). The only paper in the haemophilia literature utilising the HAP reported a mean twenty point difference between the haemophilia group and a control group tested on one occasion as per this study. However, the studies are not directly comparable due to the heterogeneous nature of the latter cohort with co-morbidities present of unknown impact in some participants such as asthma and a cardiac murmur, and marked lower limb dysfunction including total joint replacements (Fearn, et al., 2010). The current study was less heterogeneous in that the only condition defined within the inclusion criteria that could directly affect test performance was ankle arthropathy in that the stepping could have caused discomfort and reduced performance. Other conditions that might have affected aerobic cardiovascular performance were excluded. Nonetheless the results are similar and could be considered to add further weight to the supposition that aerobic fitness may be a problem in haemophilia populations.

It is interesting to note that the clinical Tecumseh step test did not produce significant results ($p = .727$). The tests differ in that the Tecumseh step test is an indicator of submaximal aerobic fitness utilising a moderate cardiovascular (CV) load and trying to minimise muscle fatigue (Reilly & Tipton, 2010) whereas the HAP survey covers a wide range of activities that have been rated from 1 to 10 METs (Metabolic Equivalent of Task where activity is considered vigorous if rated over 6 METs). These fitness results indicate that PWH are approximately as equally aerobically fit as normal volunteers at a submaximal level but that this equivalency drops away when challenged by tasks requiring higher levels of

fitness. Of course, as the HAP is a self-completed survey, this is the person's perception of their fitness, but the originating article did use an indirect calorimetric measure of maximum oxygen uptake and found that the adjusted activity score explained around 69% of measured energy expenditure variance (Daughton, et al., 1982). Therefore the researcher considers that the result could be considered a reasonable reflection of overall aerobic fitness.

Aerobic CV fitness is potentially important to the development of ankle arthropathy for two main reasons, both deriving their impact from consequent fatigue: increased injury risk and decreased musculoskeletal co-ordination. The former is perhaps the most pressing of these as correlations between fatigue and increased injury risk exist in many sports. For instance in the most commonly played sport in this study, football, it has been reported that injuries are more likely to occur in the second half of a tournament and the last 15 minutes of a game (Ekstrand, et al., 2004; Emery, 2009) when a participant is likely to be tiring. The influence of fatigue may also impact on musculoskeletal control, reaction times and sport - specific skills. Another football study noted a marked decrease in technical skills in the second half compared to the first half of the game in professional footballers (Rampinini et al., 2009). There are also a multitude of articles regarding the alteration in kinetics and kinematics of the lower limb due to fatigue (e.g. (Bisiaux & Moretto, 2008; Chappell et al., 2005; Parijat & Lockhart, 2008)). Finally fatigue can alter reaction time, at both conscious and subconscious levels, with increased time to recruit, or failure to recruit muscle groups which can lead to increased shear loading at joints (Wojtys, Wylie, & Huston, 1996).

Reduced CV fitness coupled with a tendency to greater exposure to higher risk sports (described below) is an important finding from this study data. This reduction in fitness was also reflected in the Foot and Ankle Ability Measure discussed next.

11.3.4 Foot and Ankle Ability Measure (FAAM)

This is the last measurement tool, which accurately differentiated between the HmAk group and the others. There are five ratings associated with this score representing ADL and sports domains (two each), and a global functional indicator and all were significant. The FAAM appears not to have been used in haemophilia-specific literature. As all parts of the questionnaire were equally significant and highly correlated, the researcher elected to use the sports subscale for further analysis based on its utility and representation of activities with no likelihood of a ceiling effect for younger or very fit people. A cut-off point for the FAAM sports subscale was generated with a score less than 90% indicating the likelihood of belonging to the haemophilic arthropathy of the ankle group with 90% specificity. The FAAM sports subscale can be considered of high utility due to its brevity, validated age range and use for multiple conditions (Martin, et al., 2005). It has the potential to act as a screening tool advantageous for recognising early perceived changes. It is conceivable that children might perceive changes in their running and jumping etcetera that indicate that they are not performing on a par with their peers whereas they may not notice a change to ADL (as covered by the FAAM ADL subscale). It is also beneficial that the same scale can be carried over into adulthood to monitor ongoing changes. As a functional assessment it may reflect changes at the ankle from a number of sources (or factors) such as within-foot biomechanics, altered proprioception or altered biomechanics of the lower limb impacting the foot and ankle some of which have been investigated clinically in this

study but not all were found to be statistically significant. Therefore the researcher considered that it might be of interest to investigate whether any of these factors explained membership of the FAAM group (a score of less than 90%), that was representative of HmAk group membership.

This was indeed the case with the developed logistic regression model containing “age activity begun”, HAP adjusted score and ankle lunge test explaining 53.1% of the variance in FAAM sport subscale scores and correctly classifying 80.4% of cases. However, a sizeable amount of group membership remains unexplained. This indicates to the researcher that the remaining tests representing other factors may not be sensitive enough for identifying the participant-perceived reduced function or that other factors yet to be identified are involved.

It is interesting to note that this and the other validated self-reported questionnaires performed better than the vast majority of clinical measures at distinguishing the HmAk group. There are two main arguments to explain this outcome. Firstly, all the other selected variables genuinely have no influence on the presence of HA or secondly, they do have an impact but the selected measurement tools were not the most appropriate for detection. Given that a logical consideration of several of the factors might imply that they would themselves influence the questionnaire outcome, the researcher considers that the second argument is compelling. Lobet et al. (2011) found significant associations between their choice of functional foot assessment tool and 3-D gait analysis components. The use of high-tech evaluative procedures might appear to be generally advantageous but the researcher deems that results can be difficult to interpret and apply clinically. But most importantly, the researcher considered it essential to generate clinically

applicable outcomes considering that a large proportion of PWH around the world have little access to therapy of any kind and most clinicians cannot access human movement laboratories. Being able to screen and select those needing greater input should be within the grasp of clinicians.

11.3.5 History of Injury

This factor was significant with a strong effect size however statistical analysis precluded pairwise analysis. History of previous injury is reported in the literature as a predisposing factor for sustaining recurrent injuries or new injuries (e.g. (Fulton et al., 2014; Tyler, et al., 2006)). This is thought to be associated with insufficient recovery from the first instance of injury. The researcher considers that the reasons for this to be manifold, and include: injuries not being professionally managed, rehabilitation being curtailed secondary to poor understanding or time/financial limitations from the professional or due to the person considering themselves to be fine to return to previous levels of activity.

11.3.6 Factors Differentiating People with Haemophilia from Normal Volunteers

Four factors differentiated PWH as a whole from the NV group. These are important results as previously it has been the clinical impression that there may be MSK or other differences between people who develop arthropathy and others with haemophilia but not between those with haemophilia and those without. These factors are presented in Table 11.2.

Table 11-2 Factors differentiating PWH from normal volunteers.

Haemophilia groups versus Normal Volunteers	
Calf strength	.016
Subtalar joint inversion/eversion	.0005/.001
Duration of exposure to key sport	.045

11.3.6.1 Calf strength

Calf strength was included as part of the “altered biomechanics of the lower limb” factor, and was reduced (HmAk 16.7 (out of a possible 20 repetitions), HmC 17.83 and NV 20, $p = .016$). This is the first study to present findings of an MSK difference in all PWH participants that cannot be attributed to the presence of arthropathy. Other studies in the haemophilia literature present comparison findings between PWH with known arthropathy and healthy controls making contrasts with current results problematic. The only study reporting differences between boys with haemophilia compared with healthy controls was dealing with spatiotemporal gait parameters (Bladen, et al., 2007). The results of this study reported an overall decreased walking speed compared with healthy controls. Possible explanations for this could include calf muscle weakness. Changes reported in the calf muscles in PWH with ankle arthropathy include reduced isokinetic strength (Stephensen, et al., 2012), reduced calf muscle energetic efficiency (Lobet, et al., 2012) and a reduced activation on sEMG of the medial gastrocnemius muscle belly in quiet standing (Kurz et al., 2012). The researcher proposes that the reduced DF noted in this study may influence recruitment of the triceps surae muscles resulting in a lack of control the rearfoot through its normal range in gait. This may alter the angle of pull of the muscles, a small change of which may have a significant effect on shear at the ankle joint (Scott & Winter, 1990).

The presence of ankle OA also results in alterations in calf muscle function however these results were in comparison with the contralateral healthy leg (Valderrabano, et al., 2006) and so unlike the current results cannot be said to be of an underlying nature and there were no other comparisons. A reduction in

eccentric PF torque has been identified in people with “functional ankle instability” too (Fox et al., 2008) which may be of relevance as it could indicate a lack of control of forward motion as the tibia progresses over the foot in stance phase although the relationship of the torque reduction with instability cannot be verified.

It is unknown whether any of the calf muscle findings from previous studies correlate with the calf raise test (used for calf strength testing in this study).

Potentially there is room to develop a test with good clinical utility that more closely replicates calf function in gait or other functional activity such as hopping and jumping. The results from this study add to the evidence that calf muscle function appears to deviate from normal parameters in gait and other tasks in PWH.

The reason for the calf weakness is unclear but could potentially be related to minor developmental delays such as walking later and decreased jumping ability that have been noted empirically in pre-school age boys with haemophilia. Whilst the following statement is not based on data collection in this study, and it is not possible to prove this point using the current dataset, it is possible that parental restriction of activity or pain secondary to bleeds is among the possibilities.

11.3.6.2 Subtalar joint range of motion

This is the second MSK measure that is different in PWH compared to normal volunteers. Subtalar motion is part of the “specific foot and ankle biomechanics” factor. Both subtalar inversion and eversion were reduced in PWH (inversion: HmAk 24.73°, HmC 31.03°, and NV 37.73°, eversion: HmAk 13.9°, HmC 14.63° and NV 19.2°). The researcher could not identify any haemophilia-specific papers that reported subtalar joint motion or biomechanics yet HA is reported at the subtalar joint (Tsailas & Wiedel, 2010). This study reported pure subtalar joint

inversion and eversion angulation. The axis about which this occurs, an average of 42° up from the horizontal with a wide variation (Kirby, 1987), is thought to affect lower limb loading and motion and it has been suggested that those with a lower angle are more prone to developing foot pain as this indicates a greater amount of inversion/eversion associated with a fixed amount of external/internal tibial rotation (Pierrynowski et al., 2003). The researcher finds it difficult to conceive that the whole PWH cohort has a lower axis of rotation however it may be that those who have developed HA do.

The clinical importance of this finding may be in its relationship to the gait cycle as the talocrural joint provides the larger part of motion during the early part of stance phase while the subtalar joint contributes more motion during the latter part (de Asla et al., 2006) which the researcher has proposed is the key part of the cycle. This finding when coupled with the reduction in DF range and calf muscle strength already discussed, may start to explain some of the observations noted in haemophilia biomechanical gait analysis studies such as reduced time in stance (Bladen, et al., 2007) and increased knee flexion in midstance (Stephensen, Drechsler, et al., 2009).

The reason for the presence of a reduction in subtalar joint range in the absence of frank pathology or injury is perplexing. The researcher considers that there may be three possible scenarios. Firstly, it is possible that repeated minor intra-articular subtalar bleeding from rupturing small capillaries maybe occurring secondary to normal childhood activities in particular landing from jumps or hops, leading to eventual fibrous scarring and insidious reduction of joint range. In paediatric gait the ankle joint complex is the last joint to attain adult-like kinetics (Samson, et al.,

2011) and children tend to stabilise their ankle joint rather than use it for propulsion as adults do (Samson, et al., 2009). Also adult-like sensory integration is not achieved until around 12 years of age (Peterson, et al., 2006). Finally, in the toddler, the base of support is wider which might be thought to place the foot in a more inverted position and consequently that there might be more medio-lateral shear across the yet-to-mature subtalar joint. As the toddler becomes more confident on their feet, impact forces will increase but still without adult-like impact shock absorption. Plantar pressures have been found to be highest on the heel and under the hallux in pre-school children (Kellis, 2001). These forces on an uncontrolled rearfoot may lead to minor blood vessel tearing. It is not until four years of age that plantar pressures in landing on 2 feet from a jump become adult-like (Kellis, 2001) and indeed jump-landing kinematics remain different from adults until at least 10 years of age (Hennig, Staats, & Rosenbaum, 1994). It is therefore possible that the origins of subtalar range of motion reduction lie in the normal pre-school age use of the ankle.

Secondly, there has been the suggestion that the subtalar tilt angle following acute and chronic lateral ligament injuries of the ankle is altered affecting the stability of both the ankle and the subtalar joints (Yamamoto et al., 1998). This will lead to altered joint loading and kinematics affecting the ability of the joint to move through range. The researcher considers it feasible that the majority of boys will undergo some kind of spraining manoeuvre to their ankles at some point during childhood, that may pass largely unnoticed, but it may be enough to alter joint kinematics resulting in insidious motion loss.

Thirdly, the age of the cohort should be considered. It is possible that this finding may not be present in a wholly paediatric population who have had access to good prophylactic care all of their lives. However, if subtalar motion was found still to be reduced then, the suggestion that the motion loss is secondary to normal childhood activity might have merit.

11.3.6.3 Duration of play exposure

This result refers to the number of years' exposure of the participant to the activity or sport they described as having "played" for the longest time during the period when the AC is at its most vulnerable. This is linked to the "level/intensity of physical activity" factor. Whilst there was a statistical significance between groups (HmAk 9.39 years, HmC 8.79 years and NV 10.39 years, $p = .045$), pairwise comparisons showed that only HmC to NV was significant ($p = .036$).

The approach taken to the identification of potentially key activities and exercise is unique to this study. Firstly, injury risk specific to the ankle was identified for all the activities specified (see Appendix 18), rather than utilising pre-existing generic haemophilia risk taxonomies. Secondly a key activity was identified that corresponded to the highest recorded ankle risk and the period of human development where the AC is most vulnerable. And thirdly, the total duration of exposure was utilised to recognise that damage may be cumulative. The limitation with this approach is that it relies on the accuracy of a participant's recollection and so there may be an element of recall bias. Additionally it is based on exposure-years as opposed to participant-exposures multiplied by years and unfortunately it is not possible to calculate this from the current data set. This implies that an individual's exposure may be under- or over-estimated, notwithstanding this, the

results of this study would seem to imply that the more years a person is exposed to their chosen activity the more likely they are to present with ankle joint arthropathy. Studies relating physical activity to either bleeding rate or clinical joint presentation have been published, none of the studies are specific to the ankle and so only general comparisons can be made. The most robust study appears to be that of Broderick et al. (2012) who carried out a prospective analysis associating bleed occurrence with sport or activities within the previous 48 hours. Their stratification of risky activities was based on a modification of a generic system where activities are rated according to overall likelihood of collision such that an activity was rated 2 if it was possible that a significant collision might occur and 3 if significant collisions are inevitable. Odds ratios were calculated giving a 2.7 increased risk of bleeding with a category 2 sport and a 3.4 increased risk with a category 3 sport. They concluded that for most children this represents a low overall absolute increased risk of bleeding with physical activity. Their data showed that most bleeds were not associated with physical activity and those that were appeared within an hour of participation (Broderick et al., 2012). However they also noted that HA continued to develop in the absence of activity-related bleeds. Two other studies have been published, Ross et al. (2009) in a retrospective study found no correlation between activity and joint outcome and Titinsky et al. (2009) found no correlation between physical activity and number of bleeds in children not receiving prophylaxis even though more traumatic bleeds were reported by the group taking part in strenuous activity (Ross et al., 2009; Tiktinsky et al., 2009). These studies, of various designs, present results with a theme that the activity per se does not directly affect joint health. The researcher considers that although the current study is also retrospective in nature, it does offer the advantage of some

context in which the results may be framed. From the exploratory activity data, the following data may be relevant:

- PWH members were more likely to take part in high risk activities and those in the NV group less so.
- The duration of play exposure was greater in the HmAk and NV groups.

This generates a somewhat amorphous proposition in that the HmC group is the “odd one out” here and should we be asking why the HmC group do not bleed with activity, as opposed to why the HmAk group do? This pattern is also reflected in the Beighton score. There is the potential that the HmC group (or their parents/carers) are more cautious with regards to risk taking and may have chosen less risky activities or ceased participation in risky sports if bleeds were occurring. It should also be borne in mind that the HmC group contains a range of participants with all severity of haemophilia presentations.

The median NV group duration of exposure is not significantly different from the HmAk group but the exploratory activity data indicate that they report fewer injuries associated with high risk activities (HmAk 87.5% versus NV 66.6%). This may indicate, according to the recursive theory of injury occurrence (Meeuwisse, et al., 2007), that more relevant injury-factors are present in the HmAk group. This implies to the researcher that factors may be at play that are not amenable to gross measurement or at least not the measurement methods chosen for this study. One potential is increased shear stresses present in the HmAk group secondary to poor acceleration, deceleration, landing and cutting techniques. This may result in injury to small capillaries and the subclinical bleeding proposed to be part of the HA initiation mechanism (Manco - Johnson, et al., 2007).

Whilst the haemophilia literature is ambiguous with regards to the possible correlation between physical activity and bleed generation, sport epidemiology literature is more convinced that greater exposure is a risk factor for injury. For instance in football, Dupont et al. (2010) found an increased injury risk rate of 25.6 versus 4.1 per 1000 exposure hours ($p = <.001$) when playing two matches per week rather than one (Dupont et al., 2010). For the researcher, it is hard to comprehend how exposure to risky sports over a prolonged duration could not increase the risk of arthropathy development. This would be somewhat akin to what is known as athletically accelerated aging whereby younger athletes sustain injuries more commonly seen in older populations secondary to years of repetitive microtrauma to the soft tissues (Gorse et al., 2000). With regards to the clinical management of PWH, the researcher considers that gaining a fuller understanding of activity patterns is crucial to comprehending the risk PWH are exposing themselves to in the short and long term. It may be possible to enable continued participation but with limitations on exposure time, match/game play or level of competition with a concomitant decrease in HA development.

This section has presented new MSK findings in PWH that cannot be ascribed to the presence of HA. The researcher has offered proposals for the presence of these differences and attempted to tie them into existing haemophilia research. It has also described the effects of duration of exposure to high risk activities during vulnerable developmental periods. Given that these findings appear to apply to all the PWH participants, the significance of these four factors may only become apparent when in conjunction with other factors as at the very least the MSK factors represent deviations from the norm.

11.4 Q3 To What Degree, If Any, Are Investigated Factors Related To The Presence Of Haemophilic Arthropathy?

This question looks beyond the simplicity of differences between groups to ask about the degree of influence. Moreover as the researcher has proposed from the outset that HA will only initiate when a group of factors interact to create the “right” environment, it was necessary to establish whether any of the factors tested acting together had more influence than acting individually. Simple correlation only shows strength of an association whereas regression describes the relationship in more detail but regression cannot show causation, it can only show whether variables are correlated and if so by how much. Logistic regression was utilised to satisfy these aims. To the researcher’s knowledge this is the first occasion that a regression model of non-haematological factors with the potential to influence HA development has been attempted.

In this study a model was developed that maintained an adequate ratio of variables to cohort size to ensure that the results had meaning. This resulted in the use of four variables. A model comprising the FAAM sport subscale (representative of all FAAM data), duration of exposure, ankle lunge test and subtalar inversion was statistically significant ($p < .0005$) and explained approximately 81.1% of the variance in ankle joint disease group and correctly classified 89.7% of cases.

Whilst only the FAAM and duration of exposure were statistically significant within the model, removal of the other two factors from the model resulted in a reduction in the value of pseudo- R^2 indicating that they are interacting with the other factors.

On the advice of the statistician, factors were selected for entry in to the regression process based on an iterative elimination process examining their statistical significance, represented domain, association with other potential factors and

expert opinion. This resulted in items in the functional ability, exercise/activity patterns, and range of motion (ROM) domains being included. Whilst none of these were associated with each other statistically, it should be observed that any functional ability measure score will be dependent on a number of factors including fitness, strength and ROM. Many factors from those domains that might be considered key to a well-functioning foot and ankle complex were not statistically significant in this study such as the balance measures. This lack of significance was unexpected to the researcher as empirical evidence would have seemed to have suggested otherwise. Additionally, these factors have been implicated in other chronic ankle presentations. In particular increased postural sway (de Noronha, et al., 2006; Hiller, Nightingale, et al., 2011; McKeon & Hertel, 2008) and postural control (Hiller, Nightingale, et al., 2011; McKeon & Hertel, 2008; Riemann, 2002) have been implicated. Foot posture in gait (Hiller, Nightingale, et al., 2011) and the potential that forefoot differences may be important to the development of chronic ankle problems have also been proposed (De Ridder, et al., 2013). It is possible that similar findings were not found in this study due to the choice of testing methods.

As no other study in haemophilia has investigated multiple factors on HA development it is not possible to make comparisons. Extant literature from pertinent sources, whilst looking at multiple factors, did not include the domains found here. Hubbard et al. (2007) conducted a study looking at the factors capable of predicting the presence of chronic ankle sprain (CAI). Their domains included ankle instability, postural control, isokinetic strength, lower limb alignment and dynamic balance (using the SEBT). Their testing methods were highly instrumented and a regression model identified whole foot inversion laxity, anterior

laxity of the ankle, static balance and PF to DF peak torque as predictors of CAI. Of these, only alteration of calf muscle function might be considered a finding common to both studies.

If causality can be assumed from the findings of this model, then a consideration of the mechanisms in place that might act to initiate HA is warranted. The presence of a questionnaire indicating a perceived lack of function is interesting as the reduction of function might be attributed to “a multitude of sins”; it is the perfect foil for a mechanistically-inclined researcher. The mechanisms by which the other factors in the regression model (ankle lunge test, subtalar inversion and duration of exposure) might unilaterally influence HA initiation have already been discussed as part of the response to Q2 (section 11.3). How they interact with each other to multiply their effects is a more convoluted proposition. It is easy to comprehend how ankle joint complex and subtalar factors, being directly linked segments, would affect each other’s movement and how this might alter the recruitment of the muscles charged with controlling them. It is also relatively easy to conceive of these alterations affecting the whole lower limb kinetic chain (such as compensatory pronation secondary to reduced DF which will result in increased tibial rotation that can affect the knee); all of which could affect foot and ankle function in sports and thereby the FAAM. It is more difficult to visualise how a measure of duration of exposure given in years could so greatly directly affect function on any given day. The researcher can only surmise that it represents the long term accumulation of microtrauma to the area that will increase over time unless activities are altered or ceased. How activity has been reported in this study may add some additional depth to this supposition and is discussed in the next section.

11.5 Exercise and Activity: from variety to risk

A questionnaire explored exposure to recreational activity and exercise for the entire duration of the participant's life with the purpose of addressing the exercise factors raised in the Delphi. The majority of the data has been presented in descriptive terms except for the three items derived from exposure to a key sport during childhood which were included in statistical analyses. The researcher believes that exploration of exercise and activity in this manner has not been attempted before and that these results will signpost direction for more in-depth consideration of the potential impact on HA development. In particular, whilst a clinician might intuitively consider an activity as risky, there might be little information about how or why, that is, mechanisms are missing in the evidence. An exercise may not be in and of itself an issue provided the participant is "fit for purpose" and is not abusing themselves physically such as by over training. In discussing potential activity risk, a person may expose their tissues to harm through trauma, new use, abuse, overuse, disuse or misuse (not all mutually exclusive). There are considerations of level of competition and training versus match/game play both of which increase the risk of injury (Junge et al., 2004). Broderick et al. (2015) noted that the majority of bleeds reported in their study were not associated with a sporting activity but did not preclude sports having an impact on HA development. It is feasible that there may be safe levels of exposure in terms of time and levels of competitiveness. Determining the impact of these factors may be the key to safe activity advice for PWH.

11.5.1 Activities and exercises

The data collected in this study were mainly specific to the ankle and so results cannot be generalised to all HA as, in particular, risk of injury to joints will vary depending on chosen activity. This section will first discuss the range of activities reported. It will then look at the key activity participation and injury. Finally the researcher will attempt to build a picture of how this might influence HA.

11.5.1.1 Chosen activities or exercises

This study has reported the types of activities and exercises undertaken by participants across their life time. Participants reported 57 types of activity of a wide variety from dance to climbing (see Appendix 17). This is a greater range than published elsewhere which reflects the inclusion of all recollected activities and also pastimes that cannot strictly be termed sports but are none the less active such as scouting activities. Published haemophilia literature generally reports a “snapshot” of current sports only. Possibly the closest in terms of cohort composition is a study from Ireland by Sherlock et al. (2012) although the age range is older at 16 – 63 years (N= 60). The study recorded activities reported by attendees to the national haemophilia centre over a 3 month period finding that 69% of participants were active in some form of sport or exercise. Swimming and golf were the most common pastimes. The current study found that football was clearly the most common activity for all groups. It is unclear why there would be this difference between the countries although football is less popular on the whole in Ireland. Additionally there may be differences in advice from treatment centres in the U.K. and Ireland. In the U.K. football is by far the most commonly played sport with nearly one in five taking part (Staff, 2015) and it is entrenched in the culture particularly for boys and men. Whilst it is not surprising that boys and men with

haemophilia wish to take part, the epidemiology of ankle injuries in football is such that they must be considered. A risk of injury varying between 6.52 (training) to 34.83 (match play) per 1000 exposure hours has been reported (Emery, 2010); one of the highest published in sports epidemiology literature. However, as discussed in the next section all groups are playing football but not all groups are developing arthropathy which indicates that other mechanisms must be in play. One of which, other than the severity of haemophilia presentation, may be the amount of time playing.

11.5.1.2 Duration of Exposure (also discussed above)

Sport epidemiology literature is clear that there is a link between the amount of exposure to an activity and the likelihood of sustaining injuries common to it. Moreover, there is ample evidence reporting that risk of injury increases with other aspects of exposure, namely, level of competition and training versus game exposure. The key activity identified for each participant during the articular cartilage's formative period was analysed for the effects of duration of exposure to that activity and the likelihood of having HA. It was found that the pairwise comparison between NV and HmC groups reflected a significant 1.6 hour difference in total exposure time where the HmC group exposure was less and for the HmAk group to the HmC group, the difference was not significant but was 1.14 hours, again, the HmC group figure was the lesser. Nonetheless, the researcher considers that this might represent a factor interacting in the complex mechanism of arthropathy development or perpetuation. Considering the most common key sport, football, it would appear that despite the epidemiological evidence, the sport itself is not a major influence on arthropathy development as it is played by the HmC group without obvious consequences (haemophilia severity notwithstanding).

This indicates to the researcher that the type of activity may only be important in the context of other factors which may be “exposed” by the sport resulting in more injuries, such as reduced fitness and strength. This concept is not without support as evidenced by bleeds associated with sport versus arthropathy development (Broderick, et al., 2012).

11.5.1.3 Injuries

Both looking at the reported activity data as a whole and after isolating a key activity, it can be seen that people in the HmAk group reported sustaining more injuries. In other literature, Sherlock et al. (2010) reported an injury rate of 31% in an Irish cohort, these were termed significant injuries and included fractures and joint injuries. The current study did not provide a definition for the term and so included anything that the participant judged an injury which could explain the much higher rate of injury found in this study. The injury rate for the HmAk group was significantly higher than the other groups at 60% considering all activities; almost double that of the NV group (33.63%). The association of injury history and HmAk group membership is strong concurring with published literature about injury risk factors. Literature suggests that a history of injury engenders a high risk of re-injury to the same joint or elsewhere (Bahr & Bahr, 1997; Nakagawa & Hoffman, 2004; Schneider, Bigelow, & Amoroso, 2000). This heightened risk has been assigned to insufficient rehabilitation with residual deficits in joint range, muscle strength and proprioception possible features. It is difficult in this case, as the majority of participants are adult, to understand whether the underlying reasons for injuries are secondary to a primary injury or to the underlying haemophilia, that is, PWH are misdiagnosing bleeds as injuries. Either way the implication appears clear to the researcher, with the assumption that HA development or perpetuation

is multifactorial and recursive, that improved injury prevention may reduce risk of developing it.

Injury prevention strategies would need to be predicated on the identification of the types of and/or reasons for injury. This study has identified this to a small degree but without sufficient depth of detail to make inferences beyond global statements. 47.2% of people in all groups considered their injuries to be accidental in origin. Whilst this would seem to imply that nothing could be done to prevent them, this may not be the case if the actual mechanisms were known. For instance fitter individuals may have had more energy to avoid a contact situation in the last quarter of a match. Additionally, ensuring the use of the most appropriate equipment may also prevent injury. These are examples of intrinsic and extrinsic factors affecting risk. An overview of preventative strategies in sport suggests addressing factors such as strength and fitness, shown to be reduced in the PWH participants in this study, can help prevent injuries (Schiff & O'Halloran, 2009).

This approach would also benefit the injuries designated preventable which represented 44.3% of the total. However, with all injuries, prevention cannot be directed unless an epidemiological understanding of patterns and mechanisms is gained. The researcher considers that this would be of benefit for PWH wishing to partake in sports and activities that increase risk of damage to their joints. Apart from this need, more immediately ensuring that PWH have an understanding of the risks involved in their proposed activities would seem essential. By “understanding”, the researcher intends to convey knowledge of how the body is at risk (i.e. what joint etcetera), what fitness requirements are necessary, protective equipment, appropriate footwear and skills. This information is generally available

for most sports and activities but not collated in one place or in a format that is amenable to a lay person, although a good grounding (for the clinician) on many sports may be found in the *Epidemiology of Injury in Olympic Sports* (Caine, Harmer, & Schiff, 2010). One issue is that much of the published literature refers to adult or competitive populations. Finding data regarding paediatric populations and the casual athlete is more difficult although some injury rates are available (Emery, 2003; Finch, Valuri, & Ozanne-Smith, 1998; Spinks & McClure, 2007). Discussing sport and activity with an appropriately qualified professional, such as a physiotherapist, would be advantageous to the PWH and/or their parents/carers. The researcher considers that current advice published for PWH is too generic (e.g. Anderson et al. (2005)) and does not consider the impact of lesser injuries or high levels of exposure and their potential to impact on joint health. Querol et al. (2011) concur with the researcher that a more specific approach is required (Querol et al., 2011). What this approach does not address is the PWH's attitude to activity participation and how that can impact on risk, the next section briefly reviews the study data pertaining to this area.

11.5.1.4 Risk taking

Data from the historical injury questionnaire indicates that around 50% of PWH participate in sports deemed risky to the ankle joint compared to around a third of NV group. The researcher considered the possibility that make-up of the NV group was introducing bias to the result but a review of occupations and activities indicated that this was unlikely. During these activities, the HmAk group sustained more injuries (87.5% reported injuries in high risk activities) than the HmC and NV groups (60% and 66.6% respectively). *If* the implication is that injuries contribute to HA initiation then to gain a full understanding of the differences between the HmAk

and HmC groups not only physical presentation but also psychosocial presentation needs to be understood. Following is a discussion of the potential psychosocial issues raised by the descriptive data described above. The discussion is not directly based on data collected in this study, and it is not possible to prove the points included, however the researcher has attempted to provide a clinically meaningful interpretation.

These data indicate that a number of PWH report being exercise-restricted in their early years. The activity questionnaire did not request reasons for this although it is possible to induce some. Most obviously is that joint bleeds required that there be exercise restriction for symptom control particularly in the very young who may not choose to restrict themselves. Restrictions may have also been applied in an attempt to pre-empt bleeds. This begs consideration of how much restriction is necessary and when it may become counter-productive given the loading and motion requirements for normal cartilage development (Brama, et al., 2002; Brommer, et al., 2005). Additionally, it is not only those with a history of joint bleeds that report doing less than their peers at a young age. In this case, in the absence of a bleed history, it appears possible to the researcher that unnecessary parental restriction might be present, probably born out of understandable concern for their child's welfare. When dealing with an inherited condition, consideration of the parent's experience of the condition cannot be denied. They may have direct experience of relatives with poor outcomes. The mother may be experiencing a degree of guilt for passing the condition on. In circumstances like these it might be considered that "helicopter parenting" whereby the parent exhibits a hyper-vigilance of the child (Roiphe, 2012; Schiffrin et al., 2014) is an understandable consequence.

As the child ages and progresses through the various psychosocial development stages their relationship to haemophilia will alter. It is important that haemophilia education is repeated at each developmental stage to reflect how the child will relate to their condition. In adolescence there is some clinical evidence of reduced concordance with treatment regimens and advice. Discussions with clinicians in the field raise issues of the child or adolescent's perception of having haemophilia as not a real problem as, with the exception of those who develop inhibitors, few who have been wholly managed in the U.K. will have experienced severe joint bleeds. They know they are not exactly like their peers but neither are they unwell. This raises the concept of liminality, living a borderline existence of feeling well but being vaguely under threat. Crouch and McKenzie (2006) in discussing cancer survivors propose a phase of liminality in which they yearn to feel secure and live ordinary lives (Crouch & McKenzie, 2006) which the researcher considers may be equally applicable to some PWH. Perhaps this yearning is the source of the higher numbers of PWH partaking in riskier activities; the wish or need to prove that they are just like everyone else.

Even if it is taken that liminality is an operational factor in the decision making processes of some PWH of all ages with ability to understand their condition, it does not explain the difference in injury rates described in the first paragraph between the HmAk and HmC groups when both expose themselves to risky activities. Perhaps in these cases the HmC child has adjusted well to their condition exhibiting successful coping strategies and having a secure attachment style (Ciechanowski et al., 2003) to their families and healthcare teams and liminality is less pronounced. It is possible that both child and parent may feel able to alter some risk factors associated with injury and potentially HA development

and still feel secure in their relationships with peers in particular. Additionally, perhaps if the child sustained an unpleasant bleed, the experience was enough to warrant active risk amelioration in activities. A reduction in competitive exposure where injuries are more likely to occur (Junge, et al., 2004) would be an example of this.

The implication of the above discussion for clinical management of children with haemophilia is the importance of having some knowledge of how a person at various development stages will perceive their condition, to interact with the whole family unit and ideally have a clinical psychologist monitoring the PWH family unit when they attend for their regular reviews. To re-iterate, these are the views of the researcher based on primary data originating from the historical activity questionnaire, and it is not possible to prove these points from the current dataset. However, the basic information recorded will be used to inform further investigation.

The researcher having addressed the research questions and explored the activity data will now return to the overarching research question. This final section of the discussion will bring together the researcher's reading of the results.

11.6 Summary of Findings – Responding to the Overarching Research Question

This study successfully identified a group of factors with the potential for influencing arthropathy development using expert clinical opinion and a multi-national Delphi process. This is the first study to determine that expert clinicians believe that the pathogenesis of HA is multifactorial encompassing physical, psychosocial and exercise factors alongside the haematological effects of blood in

the joint (McCarthy et al., 2015). Assessing for the presence of these in PWH with dominant ankle arthropathy was the next stage in identifying non-haematological factors potentially contributing to ankle arthropathy. A case control correlational study was used to look for relationships between the suggested factors and the presence of HA.

This study identified six tests representing factors in four domains capable of identifying people belonging to the HmAk group. This new finding reinforces the notion that the pathoaetiology of HA is multifactorial. These were: ankle lunge test (for DF ROM); CAIT; HAP; FAAM; anterior drawer test and the single leg squat test. The latter two were deemed of low utility as raw data revealed that the tests were picking up on changes due to the disease process and so would not be useful for screening purposes. Most of these tests have not been utilised in PWH previously and so direct comparison with published results has not been possible. However the HAP results do concur with previous results where it was being used for background information in a balance study with a heterogeneous cohort. Of note is the presence of 3 self-reported questionnaires in this list indicating the importance of the ability of the PWH to self-perceive symptoms which clinicians may under-value in favour of objective measurements.

Not all the factors proposed by the researcher were found to be statistically significant however plain descriptive statistics indicate that they may still be of clinical relevance. Included in this group are the Beighton score for hypermobility, 5-Point hypermobility score, grip test, great toe extension and age key sport started. Additionally the SEBT produced the most anomalous results in that people in the HmAk group consistently scored better than those in the HmC group. This

novel finding may be unique in the literature where using the test with other conditions has consistently produced poorer performance.

A logistic regression process identified a strong model from test results capable of correctly identifying 89.7% of cases. This model included the FAAM sport subscale, duration of exposure, ALT and subtalar inversion. Looking at the interaction of factors as a group has not been attempted before in HA research and regression analysis has not been used previously to develop a model for HmAk group membership. The fact that not all the factors found to be significant between groups were equally predictive in regression analysis can be attributed to sample size leading to a limit for the number of factors in the model or that they do not interact with the other included factors to affect HmAk group membership. Their lack of significance in the regression model does not imply a lack of clinical relevance.

The overarching question asks “in what ways” factors contribute to HA development and the relevance of these study results could be questioned given the age range of the study was 12 – 50 years whilst arthropathy development begins in childhood. It could also be argued that a prospective cohort study should have been the chosen study design following children with haemophilia and regularly recording various parameters over a number of years and noting which of the cohort developed arthropathy. However without the current study in people already presenting with ankle HA, it would be difficult to identify which variables to monitor as there is no supporting literature. Therefore the relevance of the results and findings of this study programme is that it will now enable guided and focussed investigation in paediatric cohorts with a greater chance of improving our

understanding of the mechanisms of HA development. In the meantime, clinicians have been presented with a group of malleable factors that may influence HA development that they may, with some justification, monitor in children.

The researcher may discuss the results from the study as if the implication of the model is causality, the caveat being the “if” and although the study has successfully identified factors capable of identifying members of the HmAk group, causality with respect to HA development has not been demonstrated and may only be demonstrated by means of prospective study in a paediatric cohort. With regards to the mechanisms of HA causation, the only conclusion that may be drawn is the likelihood that factors interact is high. The FAAM result was highly significant. As this represents a functional self-assessment of foot and ankle performance it can be inferred that factors capable of affecting function will interact to alter this score. This research programme was approached with two framing theories:

1. The development of HA is complex and potentially driven by non-haematological factors with the ability to alter loading of the ankle articular cartilage
2. This process is recursive in nature and that the risk of arthropathy development would be individual and actual risk of causing harm to the joint would vary on a daily basis dependent on factors present.

The researcher would argue that these results support these theories. Furthermore the researcher argued that these factors might be intrinsic to the person (such as their MSK health) or extrinsic (such as exercise choices or weather conditions) and that only by way of interaction of these factors would a situation occur where HA

would initiate. Determining the exact complex mechanisms of increasing risk for arthropathy development may be beyond any research design, however, identification of factors without knowing their exact mechanism of operation is still clinically valuable as risk may be ameliorated by removing their relative influence. Figure 11.1 gives an illustration to how this might work. An inciting event will only occur if all five links in the chain are present. Removing any one link may prevent a context from developing whereby AC insult occurs and HA develops.

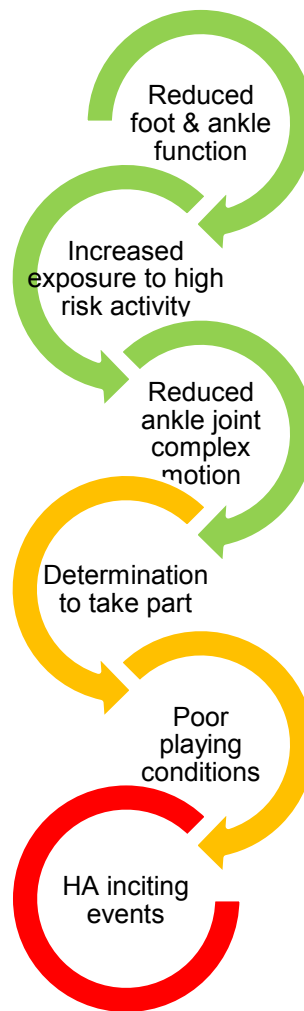


Figure 11-1 An illustration of the potential interaction effects of factors influencing HA

The clinical practice implication of this is the ability of clinicians to assess for the presence of factors hereby identified and to put into place pre-habilitation where possible to reduce their impact on HA development.

A paradigm shift in the activity and sport education of PWH and the parents/carers is needed in order for them to consider cumulative rather than absolute risk. Even though this study did not indicate that PWH were avoiding any kinds of activity except for those deemed particularly harmful, there was a sense of being less active than peers particularly at younger ages. An improved understanding of the mechanistic risks of injury may be enabling for parents of PWH so that they feel more comfortable with their child joining in. In some ways, applying these individualised interventions and using the PWH's self-perception of their performance may be the best prospective way of determining impact on HA initiation.

11.7 Discussion of the Assessment

It was the researcher's intention to highlight those at risk of HA of the ankle using clinically applicable tools. Overall the researcher considers that the protocol has been successful in this with the only qualification to that statement being reluctance on the part of some potential participants due to the length of the process. It was therefore necessary to perform this interim analysis to facilitate rationalisation of the protocol in order to expedite recruitment without removing tests that might prove to be important. This may now be achieved by removing tests found to be not valuable (Anterior Drawer Test, Single Leg Squat test and Tecumseh Step test) or those having high associations with other tests (SEBT mean scores). This

rationalised assessment protocol will be used in the ongoing study. Whilst the chosen protocol and indeed study design have been generally successful they do have some limitations which will be discussed in the next section.

11.7.1 Limitations of the Study

This study like others has limitations which can be divided into the following areas.

11.7.1.1 Participants

The researcher acknowledges that all groups represent convenience sampling and so may be subject to selection bias. However, the researcher considers this to be unavoidable as across the whole of the U.K. there are only around 2,400 people with severe haemophilia (UKHCDO, 2015) many of whom would not meet either inclusion or exclusion criteria and so random sampling was precluded. The researcher attempted to ensure that the cohort was multi-ethnic and representative of all severities of haemophilia. The groups were not age-matched. Again this was due to the limited participation pool although again the researcher attempted to ameliorate this with broadly matching the groups as a whole.

It is possible that there is a sample bias present in the NV group as recruits were mainly staff from the host NHS trust. A number of these were physiotherapists who might be considered to be unusually fit and active however a review of the raw data did not reveal any particular differences in data sets between the various staffing groups.

The inclusion criteria required that the HmAk group members ideally had unilateral ankle arthropathy. However, this would have reduced the pool of participants markedly as many have a bilateral presentation. Therefore, bilateral presentations were accepted as long as the participant could clearly identify a “worse” ankle. This

approach has been used elsewhere in the literature when examining chronic ankle instability (Hubbard, et al., 2007).

11.7.1.2 Study design

The overall design for this research programme was a mixed-methods design however the majority of data presented in this thesis are quantitative in nature. The qualitative data presented are minimal and originated mainly from the Delphi study but is enough to meet requirements to identify this study as mixed methods. Overall in this ongoing research programme additional qualitative data will be collected in a further study protocol by the inclusion of a sub-set interview taking inspiration from the activity questionnaire to gain further depth and insight into activity and exercise choices.

11.7.1.3 Logistics of the Study

The study was necessarily multi-centred due to the nature of the condition and the participating centres which are geographically dispersed across England. This means that multiple investigators have taken part. All investigators were experienced physiotherapists with master's-level training. Inter-rater reliability has not been undertaken as this was logistically impossible to achieve. However the researcher endeavoured to reduce impact of this by acting as gold-standard for all tests and ensuring that investigators were performing tests in a standardised manner. The tests most likely to be affected by reliability issues are those with a degree of subjectivity: anterior drawer test, goniometric measures, Single Leg Squat test and Foot Posture Index. An extensive "standard operating procedures" manual was provided along with published instructions where available.

Beneficially, two of these more subjective tests will be eliminated from the rationalised assessment protocol.

11.7.1.4 Assessment instruments

Finally the sensitivity of the clinical tools may be a limitation of the study. Some factors that the researcher and other expert clinicians thought might be strong contenders for influential factors were not significant. It cannot be determined whether this is fact, a reflection of the chosen measurement tool or of sample size. The researcher had decided to only use measurement tools that can be implemented with minimal cost and equipment to reflect the lack of parity of haemophilia care across the world. The downside of this approach was the possibility of not detecting differences that more sensitive equipment might have detected. Having said this, the researcher considers that laboratory based measurement is frequently not clinically applicable and requires some form a transformation for use.

The questionnaires utilised were all self-reported, the implication being that the reported symptoms and function are not verified, however, this limitation is ameliorated to a degree by some of the clinical tests. Although in some cases results of factors from the same domain are not equally statistically significant, such as the HAP and Tecumseh step test, a closer analysis of the situation shows that both tests show good fitness at submaximal levels (which is the maximum available from the step test). It has been suggested that self-report may be biased or affected by variables such as psychological or sociological status and also by comprehension (Harrison, McLaughlin, & Coalter, 1996). This position has been countered by the suggestion that things that are perceptual by nature like the way

a joint feels and can only be measured by asking the person (Schmitt, 1994; Spector, 1994).

The novel activity questionnaire purposely designed to respond to factors raised by the Delphi process, required the use of distant recall and may be subject to recall bias. It has been suggested that care must be taken when collecting data retrospectively. This is mainly an issue where the participant is asked to recollect exposure to something that may be directly causative to a condition as it may affect the null hypothesis. It is considered important that all participants are exposed to standardised assessment procedures. It is also considered beneficial if a “control” group can be included from within the same condition population (Kopec & Esdaile, 1990). In this case, a haemophilia control has been included for this purpose. The researcher considers that if recall bias is present in this study it is likely to be equivalent across all groups and so its effects will be comparable.

One of the assessment “instruments” was the medical records of the PWH for collection of background haematological data, however it has proved difficult to source this information equally from all haemophilia centres due to differing record keeping systems. Additionally, childhood information was not always available in adult centres if the person had transferred there from elsewhere. This has led to a limited ability to analyse the significance of these factors. It may be necessary to contact the participants again to attempt to retrieve some of the missing data.

Overall, the limitations described here should to be considered when reflecting on the generalisability and transferability of the findings to the general haemophilia population.

11.8 Summary

From the original 17 Delphi factors actively investigated, measures representing seven factors have been found to be important in predicting the presence of HA at the ankle. These were:

Altered lower limb biomechanics, Physical activity choices,
Specific foot and ankle biomechanics, Level/intensity of physical activity,
Reduced general fitness, Growth stage appropriate activity,
Proprioceptive deficits.

Although factors with the potential to influence arthropathy development have been identified, mechanisms for their action have not been explored and this will need to be addressed where possible. Only by gaining a greater perspective on the potential factors and the ways in which they might interact can healthcare professionals help to limit the impact of HA in the lives of PWH. The thesis concludes by examining the guidance provided by these results for future research directions.

Chapter 12 Summary of Thesis, Contribution to Knowledge, Suggestions for Future Work and Conclusions

12.1 Thesis summary and overview

The purpose of this thesis was to investigate the multifactorial nature of the development of HA with the intention of gaining an improved understanding of the condition's pathogenesis, identifying tools that could help in the recognition of early joint disease, and helping in the screening of PWH at risk.

The first stage of the study established factors that an International, multi-professional panel of haemophilia experts believed could influence HA development at the ankle using a Delphi Process. Forty-two factors in four categories reached consensus and were rationalised down to 22 through a feasibility process, to focus onward investigation to the influence of musculoskeletal (MSK) and physical activity factors. The researcher chose to ensure that the results of any onward investigation had high and immediate clinical utility by limiting measurement tools to those with equally high clinical utility in order to ensure equitable access to all clinicians. A review of the potential tools indicated that some preliminary work was required and in particular the chosen tool for assessment of dynamic balance, the SEBT, did not have published information regarding gluteal muscle activation. Therefore a sEMG study was carried out assessing the activation of the glutei medius and maximus in performing the full SEBT protocol. The results of this study indicated that the posterior and posteromedial reach directions resulted in the greatest activation. In addition to assisting the researcher in identifying the best test protocol to apply to PWH, these

results also provide the wider clinical community with an increased knowledge base regarding the SEBT on which to base their testing and training protocols. The method for assessment in the case-control study was derived from these results, together with other published literature on the test, in order to ensure the most appropriate composition was used for the haemophilia cohorts. With regards to the suggested exercise factors, it became apparent that none of the published assessment tools would satisfy purpose and so a novel exploratory questionnaire was developed and piloted.

Having set the full protocol for investigation, a case-control correlational study was undertaken. Three groups, PWH with ankle arthropathy (HmAk), PWH with no joint disease (HmC) and normal volunteers (NV), underwent assessment for 18 MSK, exercise and occupation factors. Background medical data constituted information on a further 4 factors; these were not actively investigated.

The use of a mechanistic-basis of approach to the overall research question had not been attempted in haemophilia research before. Further, investigating the potential for multiple factors to conflate in their action is unique to this study in terms of published haemophilia literature; considering the subject area, the range of factors under investigation and the data analysis processes. The researcher considered that only by gaining an understanding of the inter-play of factors could the differences in PWH that determine who develops HA, be interpreted. The results of this study present a unique perspective of HA development with the potential to influence preventative and management strategies. Presentations and publications relating to this study programme are presented in Appendix 18.

12.2 Contributions to Knowledge

This section delineates the key contributions of the study programme described in the thesis summary above. Contributions are presented for each study. Overall, it should be noted that this is the first study into the pathogenesis of HA of the ankle to undertake a mechanistic mixed methods approach acknowledging the complexity of arthropathy development.

The Delphi study:

- First international, multi professional consensus exercise on the potential for non-haematological factors to affect the development of HA at the ankle in which the panel concluded that the pathogenesis was likely to be multifactorial with a wide range of potential contributory factors.

SEBT electromyography study:

- This small but generalisable study is the first to present the activity of the gluteal muscles in all eight reach directions, finding that the posterior reach direction produced greatest muscle activity, a direction not tested in the only other study published in the area.
- Together with other published data on the SEBT this allows the clinician to select a fully individualised assessment and training protocol using this tool.

Case-control study:

- First study in the HA arena to investigate non-haematological factors concurrently in order to assess their interactive effects, identifying a group of factors on univariate analysis correlating with the presence of ankle joint arthropathy. These were: Ankle Lunge Test, Foot and Ankle Ability Measure

(FAAM), Cumberland Ankle Instability Tool (CAIT), Human Activity Profile (adjusted score) (HAP).

- The clinical test, Ankle Lunge Test, showed that PWH with early ankle arthropathy had reduced ankle DF.
- Three self-reported test instruments showed that PWH demonstrated lower scores, indicating poorer performance, for ankle instability (CAIT), foot and ankle function (FAAM), and overall aerobic fitness (HAP).
- This study also indicated that self-perception of the symptoms of HA may be a better indicator of joint health than currently used/available clinical tools.
- First study to identify musculoskeletal factors that differentiated PWH from normal volunteers (subtalar joint inversion and eversion, and calf strength) that cannot be associated with the presence of joint disease.
- It is the first study in haemophilia to indicate that the duration of exposure to chosen activities may be more important than the activity itself in the development of arthropathy.
- First study in haemophilia to develop a regression model to help explain membership of the haemophilia ankle group which consisted of: FAAM sport subscale, duration of exposure to key activity measures, ankle lunge test and subtalar inversion. The first two factors were significant in the model.
- Identification of the model where four factors have been shown to interact statistically (model weakens with the removal of any factor) supports the researcher's conceptual framework of a recursive pathway to arthropathy initiation or perpetuation comprising of factors that have the capability to affect loading and control of the ankle joint complex.

- For each additional year of exposure to the participant's key sport, the odds of being in the HmAk group increased by 1.8 (1.04 – 3.01).
- For each unit reduction in the FAAM sport subscale, the odds of being in the HmAk group increased by 1.21 (1.07 – 1.36).
- A haemophilia-specific cut-off of less than 90% for the FAAM sport subscale in order to facilitate its use as a screening tool was identified.
- A wider range of activities was identified than previously reported indicating that PWH are avoiding only sports deemed truly dangerous due to the likelihood of catastrophic injury.
- Possibility of risk-taking behaviour with respect to activity selection in PWH was identified.
- A higher rate of injury was identified in the HmAk group when taking part in activities and exercise than in the HmC and NV groups.
- Recognition of the need for improved exercise and activity education for PWH, their families and clinicians, in particular with regards to cumulative risk and exposure time.

In line with the pragmatic principles underlying this thesis, the researcher considered that the data generated from the studies presented in this document has produced warranted assertions. That is, they are true insofar as they are deemed fair and comparable to extant literature where it exists.

12.3 Clinical Implications

Whilst it must be acknowledged that the results of this study do not represent any causality of HA development, they do signify reasonable indicators of HmAk group

membership and so clinicians may choose to assess their clients for their presence. Improving the presence of any biomechanical or other deficits can only be of benefit to PWH in improving joint load patterns and improving exercise tolerance. It is possible that this approach will lead to an amelioration of factors conflating to initiate or perpetuate HA. For boys with haemophilia, buy-in to pre-habilitaton could be facilitated by couching the training programme as activity skills acquisition which should ultimately improve their performance in their chosen activity.

The researcher is satisfied that these results have been achieved without the use of highly technical or expensive equipment meaning that clinicians can gain some immediate clinical benefit from results.

12.4 Ongoing Work

In the introduction to this thesis, the researcher indicated that the research programme had grown beyond the confines of the doctoral programme of work. This is reflected by the continuation of data collection for this study. It is intended that the haemophilia group samples be doubled and a fourth group: ankle-problems with no haemophilia added, in order to strengthen and validate the results of this interim data collection. A rationalised assessment protocol will be implemented removing tests found to be not useful (Anterior Drawer Test, Single Leg Squat test and Tecumseh Step test), rationalising the method for the SEBT to only collecting the maximum measure, but retaining all other measures to determine whether increasing group size affects results, such as for the hypermobility measures where descriptive differences were noted between groups that were not statistically significant, and for great toe extension which was the only

other item approaching statistical significance. Additionally, an interview protocol will be developed from the activity questionnaire data potentially to evaluate how PWH approach their exercises choices with respect to risk.

12.5 Suggestions for Further Work

The ultimate positive outcome for this study programme would be to develop a screening model for young boys with haemophilia in the hope of identifying and ameliorating risk of developing HA. Given the model already developed, the next stage for approaching this might be testing it by applying it to a cohort of PWH with known HA at the ankle. The following research question might be applied:

What are the odds of someone presenting with ankle arthropathy given a presentation with FAAM sport subscale score of less than 90%, Duration of exposure to their key sport of X, ankle lunge test measure Y and Subtalar inversion range of Z?

If the model predicts the ankle arthropathy likelihood better than chance, then it can called fit for use in the general haemophilia population, and could be utilised by the haemophilia community to monitor the progression of their patients. The data for the ankle lunge test and subtalar inversion needs to be evaluated to try to identify cut-off values for those measures. Additionally, further investigation is required into what constitutes safe duration of exposure of physical activity in order to establish a cut-off point.

Football may be the perfect paradigm to begin with given its popularity.

Furthermore, the exposure measure needs to be refined into something more immediate, such as number of hours played each week, as although the duration

of exposure is a very strong indicator, it is measured in years and is retrospective. Developing a programme for boys with haemophilia to reduce their injury risk within football (and other sports) by utilising skills and fitness training would also be beneficial. The impact of this training could be prospectively monitored for its impact on level of injury.

Other directions for future research could be separated into MSK specific, exercise and injury specific, generic haemophilia and miscellaneous.

12.5.1 MSK specific

A challenging project would be to investigate why there are subtalar changes in PWH and do those going on to develop ankle HA have a low axis at that articulation, as a reliable method would have to be determined to identify the axis. Developing an improved tool to assess calf muscle function and determining the effects of calf muscle weakness on gait, running and landing would be beneficial. With respect to hypermobility, developing a haemophilia-specific tool to determine its presence would help ascertain if there are any links to HA development.

12.5.2 Activity specific

Gaining a deeper understanding for PWH's activity choices would help clinicians develop appropriate education and advice. Specific factors that warrant further investigation include determining safe exercise dosage for risky activities and identifying injury mechanisms so that preventative actions can take place. Further, identifying joint-specific risk levels would be advantageous. Prospective study of the application of preventative measures could take place.

12.5.3 Generic haemophilia

From a psychosocial perspective, the identification of risk taking behaviour warrants further investigation as this could lead to improved psychosocial care and education.

There are studies that could continue to address factors not incorporated into this study such as an investigation into footwear patterns in PWH or investigation into PWH and clinicians beliefs about rehabilitation in haemophilia care.

Ultimately, the research programme has generated a wealth of data that has produced some unique and clinically applicable findings, and also produced many new questions.

12.6 Conclusion

In conclusion, this mixed-methods study has presented a number of new and exciting findings which have supported the researcher's premise that the development of HA at the ankle is not only multi-factorial but is dependent on the interaction of a group of factors representing several domains. Additionally, the results from this study programme have added to the hitherto incomplete pathophysiological picture of the development of HA. A strong regression model has been developed that identified the FAAM sports subscale and duration of exposure to a key sport between 3 and 16 years of age as independent variables with the strongest association with HA at the ankle. The components of this model are amenable to physiotherapeutic intervention both through addressing physical deficiencies that influence function, and through education and advice regarding exercise choices. This indicates that physiotherapy can play an important role in

the prevention of HA by reducing the risk of factor interaction and thereby lessening the potential for the development of HA. These findings will enable physiotherapists to screen for those PWH at high risk of developing HA at the ankle. Identification of an arthropathy phenotype in PWH appears more achievable on the basis of these results.

Chapter 13 References

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Appendix 1. Delphi Process Ethical Permission Letter



Health Research Authority

NRES Committee South East Coast - Kent

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09 October 2012 (reissued 26/10/2012)

Dr Pratima Chowdary
Consultant Haematologist, The KD Haemophilia centre & thrombosis unit
Royal Free London NHS Foundation Trust
The KD Haemophilia centre & thrombosis unit
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NW3 2QG

Dear Dr Chowdary

Study title: An Exploratory Study for Developing an Assessment Instrument for Evaluation of Non-Haematological Factors and their Effect on the Development of Joint Disease in Haemophilia.

REC reference: 12/LO/1137

Protocol number: N/A

Thank you for your letter of 23 August 2012, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of

the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at <http://www.rdforum.nhs.uk>.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Covering Letter		09 June 2012
Investigator CV	Pratima Chowdary	
Letter of invitation to participant		
Other: CV: Ann McCarthy		
Other: CV: Ann P Moore		
Other: CV: LA Redhead		
Other: Study Flow Chart		
Participant Consent Form	0..02	10 May 2012
Participant Consent Form: 12-17 Years Old	0.02	27 July 2012
Participant Consent Form: Parental	0.02	03 May 2012
Participant Information Sheet: Expert Clinician	0.02	27 July 2012
Participant Information Sheet: Expert Patient	0.02	27 July 2012
Participant Information Sheet: Parents	0.04	27 July 2012
Participant Information Sheet: Adults	0.04	27 July 2010
Participant Information Sheet: Young Person's	0.04	27 July 2012
Protocol	1.4	11 June 2012
REC application	100937/3372 01/1/945	19 June 2012
Response to Request for Further Information		23 August 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for

Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “*After ethical review – guidance for researchers*” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/LO/1137	Please quote this number on all correspondence
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With the Committee's best wishes for the success of this project

Yours sincerely

Handwritten signature of Dr Ray Godfrey, consisting of the initials 'PP' followed by a cursive signature.

Dr Ray Godfrey
Chair

Email: NRESCommittee.SECOast-BrightonandSussex@nhs.net

Enclosures: “After ethical review – guidance for researchers”

Copy to: Hameedah Bogle-Dawoud, Royal Free London NHS Foundation Trust

Appendix 2. Delphi Process: Round 2 Survey

Establishing the non-haemophilia factors that may affect bleeding - 2nd round

Welcome back Delphi Participant and thank you for continuing with the survey!

This is truly an international study with participants from 10 countries and clinicians from all professions represented. The first round data was extremely interesting and could broadly be broken down into 4 groups:

1. Physical factors intrinsic to the person
2. Factors extrinsic to the person affecting their physical well being
3. Factors to do with compliance, education and accessing medical management
4. Factors innate to the underlying haematology

In this round, we are asking you to consider and rate the importance of the proposed factors with respect to their potential to influence the development of haemarthropathy at the ankle. When rating these factors, please remember that the emphasis of this project is the ankle joint.

Below you will find the list of proposed factors grouped as indicated above. There is also a definition of the factor derived from round 1 data. Where there were several closely related suggestions, an umbrella term has been chosen which we hope encompasses all the variations on the theme. If however, you feel that something important is missing, there is also space to add further comment at the end of the survey.

This information will be collated and checked for consensus/agreement. The occurrence of any further round is dependant on these results.

Thanks once more.

Kind regards,

Ann McCarthy
Physiotherapy PhD Student, Katherine Dormandy Haemophilia Centre, Royal Free London NHS Foundation Trust

Supervisors
Professor Ann Moore, Centre for Clinical Research, University of Brighton
Dr Pratima Chowdary, Katherine Dormandy Haemophilia Centre, Royal Free London NHS Foundation Trust
Dr Lucy Redhead, School for Health Professions, University of Brighton

Establishing the non-haemophilia factors that may affect bleeding - 2nd round

This section is to do with factors intrinsic to the person.

For each factor, please indicate how important you feel its influence is on the development of ankle haemarthropathy.

* 3. Younger Age

This factor reflects the activity levels of a child and inability to express any sense of discomfort in the ankle at a young age.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Younger Age	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 4. Altered Biomechanics of lower limb affecting the foot/ankle

Non-ideal motion and control of the lower limb above the ankle leading to increased stress at the ankle possibly due to shortened/tightened/weakened muscles, loss of joint range or uncontrolled movement.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Altered Biomechanics of lower limb affecting the foot/ankle	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 5. History - trauma

History of trauma to the ankle may leave it vulnerable to further trauma or leave it in a condition susceptible to bleeding. For instance acquired ligamentous laxity/insufficiency, osteochondral damage or capsular damage.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
History - trauma	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 6. Age - developmental maturity

At certain points the child is unable, due to neuro-developmental status, to perform functionally as well as an adult leading to an increased risk of injury. For instance they will have poorer balance, ligamentous laxity, less developed motor strategies and increased motion at joints.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Age - developmental maturity	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 7. Joint already a target joint for bleeds

The ankle joint itself has already become a target joint (has experienced several previous bleeds) and so bleeds more easily.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Joint already a target joint for bleeds	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 8. Aging

An adult is more susceptible to joint damage as a factor of advancing age.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Aging	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 9. Adjacent joint arthropathy

Joints more proximal in the leg, e.g. the knee, have developed arthropathy thereby altering the stresses at the ankle altering the biomechanics. This can lead to gait dysfunction.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Adjacent joint arthropathy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 10. Limb dominance

More bleeds may occur in the dominant limb.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Limb dominance	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 11. Other condition-specific developmental issues

For example dyspraxia secondary to inter-cranial haemorrhage, could lead to abnormal loading of the ankle joint and so increased risk.

	Not at all important	Low importance	Slightly important	Moderately important	very important	Extremely important
Other condition-specific developmental issues	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

It is suggested that other concurrent conditions may affect the presentation of haemophilia such as osteoarthritis, cerebral palsy, Charcot-Marie-Tooth or multiple sclerosis.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Neuromuscular conditions present	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 13. Age – growth spurts

During a growth spurt, the child's rate of bone growth out-strips the lengthening of muscles and tendons, resulting in what should be temporary alterations such as shortened muscles and weaker ligaments.

	Not all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Age – growth spurts	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 14. Primary hypermobility

Primary generalised congenital hypermobility is associated with increased instability, reduced muscular support and increased risk of inversion sprain making joints less stable and more at risk.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Primary hypermobility	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 15. Proprioceptive deficits

Reduced proprioceptive abilities such as decreased feedback/ feed forward reaction times (linked to uncontrolled movement), foot placement errors in gait, and reduced balance leading to increased likelihood of injury.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Proprioceptive deficits	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 16. Reduced general fitness

Physical activities may strengthen the muscles to support the joints. It may also improve proprioceptive development thereby providing a protective response against minor injury.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Reduced general fitness	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Establishing the non-haemophilia factors that may affect bleeding - 2nd round

This section is to do with factors extrinsic to the person.

For each factor, please indicate how important you feel its influence is on the development of ankle haemarthropathy.

* 17. Surfaces used for exercise purposes

There is some evidence that exercise surface can affect risk of injury. Uneven surfaces could result in loss of balance. Harder ground could lead to increase stresses on the joint.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Surfaces used for exercise purposes	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 18. Faulty exercise/activity training methods

Overtraining, undertraining or training wrongly for a specific activity.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Faulty exercise/activity training methods	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 19. Footwear choices

Factors such as shock absorption, lack of impact modulation and lack of support within the shoe itself, shoe fashions and not selecting sport-appropriate footwear could adversely affect ankle function.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Footwear choices	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 20. Growth stage and appropriate activity

A lack of appropriate activity whilst growing could result in reduced development of proprioception and conditioning (general physical fitness). Also poorer functional control during growth spurts as demonstrated by poor muscle control may increase the risk of injury. This may indicate that avoiding sports requiring high levels of motor control may be beneficial.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Growth stage and appropriate activity	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 21. Lack of protective equipment for chosen activity

Increased risk of trauma without the appropriate equipment for the activity/exercise.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Lack of protective equipment for chosen activity	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 22. Level/intensity of physical activity

High level activity or highly intensive activity might lead to subclinical bleeding within the weightbearing joints. Also, plainly suggested that those who exercise more sustain more bleeds.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Level/intensity of physical activity	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 23. Ankle injury prevalence within the population

It is proposed that the activity levels within the haemophilia population have normalised and the prevalence of ankle disease reflects the fact that the ankle is one of the most commonly injured joints.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Ankle injury prevalence within the population	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 24. Occupational/vocational choices

Jobs requiring heaving lifting or prolonged standing may increase ankle loading and so risk of bleeding.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Occupational/vocational choices	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 25. Physical activity choices

Choosing to play sports with inherent risk of lower limb injury (e.g. football, basketball, scootering, trampolining and ice hockey) will increase overall risk of ankle bleed. Also, increases overall impact loading on the joint.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Physical activity choices	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 26. Repetitive action in daily life

It is suggested that normal low load repetition such as when driving may be enough to overload the ankle joint leading to bleeding.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Repetitive action in daily life	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 27. Unprotected motion in affected joint

In an already affected joint with thickened synovium, normal motion could result in synovial pinching and thereby more bleeding.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Unprotected motion in affected joint	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 28. Cigarette smoking

It is suggested that smoking is proinflammatory

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Cigarette smoking	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Establishing the non-haemophilia factors that may affect bleeding - 2nd round

This section is broadly to do with compliance, education and non-haematological management.

For each factor, please indicate how important you feel its influence is on the development of ankle haemarthropathy.

*** 29. Poor adherence to treatment regimen**

Bleeds resulting from not adhering to recommended prophylactic regimen & so circulating factors not high enough to cope with demands.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Poor adherence to treatment regimen	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

*** 30. Poor adherence to rehabilitation programmes**

It is proposed that incomplete rehabilitation leads to persistent weakness, altered motor control strategies and a return to activities without being fully fit which may ultimately result in further injuries.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Poor adherence to rehabilitation programmes	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

*** 31. Early effective bleed management**

This reflects the education of the patient/carers and includes issues such as recognising a bleed, how soon and how long to continue factor replacement treatment and when to seek advice. Additionally, how long to rest and how much to restrict weightbearing post-bleed.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Early effective bleed management	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

*** 32. Growth-appropriate factor regimen**

Growing children need adequate cover and this varies. Should there be further cover during growth spurts considering the additional biomechanical stresses that exist that may not be taken into account by the current calculations for treatment dose?

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Growth-appropriate factor regimen	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 33. Haemorrhage enhancing medications

The potential of medications for other conditions to directly affect the propensity to bleed.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Haemorrhage enhancing medications	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 34. Global ineffective patient education

Patients showing evidence of a basic lack of understanding of how to manage their condition such as timing their prophylaxis to be most effective at times of day when activity is greatest. Also a generational issue whereby patients born in the era of prophylaxis have not known what it is to experience joint bleeds regularly and so exhibit disbelief or possibly denial about their condition.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Global ineffective patient education	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 35. Identification and treatment of chronic synovitis

Lack of consensus on how to deal with this clinical sequela which is known to increase the rate of bleeds and subclinical bleeding.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Identification and treatment of chronic synovitis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 36. Practitioner not ensuring effective rehabilitation

It is proposed that without full rehabilitation there is a risk of reduced power and proprioception which may result in further injuries. It is also suggested that rehabilitation is neglected where bleeds are less severe.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Practitioner not ensuring effective rehabilitation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 37. Lack access to treatment

Due to geographical or financial issues, patients are unable to access either the management advice/support that they require or the actual factor replacement due to local health care systems.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Lack access to treatment	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 38. Non-weight bearing during bleed

This was proposed to be a known factor for increasing cartilage damage.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Non-weight bearing during bleed	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Establishing the non-haemophilia factors that may affect bleeding - 2nd round

This section is to with the underlying haematology and its management.

For each factor, please indicate how important you feel its influence is on the development of ankle haemarthropathy.

* 39. Bleeding before prophylaxis

This represents those who with no family history and therefore are only diagnosed after bleeding has occurred or clinicians accepting minor bleeds into the ankle prior to beginning prophylaxis

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Bleeding before prophylaxis	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 40. Number of bleeds in a joint

It is suggested that this may have a degree of correlation with development of arthropathy. It is suggested that this is the main cause of synovitis and arthropathy.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Number of bleeds in a joint	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 41. Levels of factor VIII/IX

This defines the severity of the haemophilia. It is expected that a person with the lowest levels of circulating factor levels will result in an increased rate of bleeding.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Levels of factor VIII/IX	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 42. Inhibitor formation

This affects the efficacy of the factor replacement regimen and so will result in an increased risk of bleeding.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Inhibitor formation	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 43. Genetic propensity to joint damage

Such as autoimmune conditions, altered immune responses, connective tissue diseases and altered inflammatory responses.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Genetic propensity to joint damage	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 44. Sub-clinical bleeding

There is a suggestion that sub-clinical bleeding occurs more than is realised through normal daily use due to the high load and activity of the ankle joint.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Sub-clinical bleeding	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 45. Sufficiency of factor regime

There is a suggestion that early bleeds are not treated aggressively enough. This also represents the suggestion that the current dosing regimens are not adequate for everyone.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Sufficiency of factor regime	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 46. Type of factor treatment regimen

It is suggested that using prophylaxis over on-demand regimens will influence the occurrence of bleeding.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Type of factor treatment regimen	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

* 47. Bleeding phenotype

It is known that mild haemophiliacs can have significant bleeds and severe haemophiliacs can have few bleeds. It is suggested that this is associated with gene mutations. Additionally, those with more bleeding can have no apparent consequences to their joints and those with minor bleeds can present with far reaching consequences.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Bleeding phenotype	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

48. We'd like to offer you the opportunity to comment if you would like to. Do you have any feedback on the survey design and process? Or, has completing this survey brought to light any other factor that you feel is missing? Any other feedback is welcome.

Appendix 3. Delphi Process: Complete factor list with rationales

Factor	Rationale
INTRINSIC MUSCULOSKELETAL FACTORS	
Younger Age	This factor reflects the activity levels of a child and inability to express any sense of discomfort in the ankle at a young age.
Altered Biomechanics of lower limb affecting the foot/ankle	Non-ideal motion and control of the lower limb above the ankle leading to increased stress at the ankle possibly due to shortened/tightened/weakened muscles, loss of joint range or uncontrolled movement.
History - trauma	History of trauma to the ankle may leave it vulnerable to further trauma or leave it in a condition susceptible to bleeding. For instance acquired ligamentous laxity/insufficiency, osteochondral damage or capsular damage.
Age - developmental maturity	At certain points the child is unable, due to neuro-developmental status, to perform functionally as well as an adult leading to an increased risk of injury. For instance they will have poorer balance, ligamentous laxity, less developed motor strategies and increased motion at joints.
Joint already a target joint for bleeds	The ankle joint itself has already become a target joint (has experienced several previous bleeds) and so bleeds more easily.
Aging	An adult is more susceptible to joint damage as a factor of advancing age.
Adjacent joint arthropathy	Joints more proximal in the leg, e.g. the knee, have developed arthropathy thereby altering the stresses at the ankle altering the biomechanics. This can lead to gait dysfunction.
Limb dominance	More bleeds may occur in the dominant limb.
Other condition-specific developmental issues	For example dyspraxia secondary to inter-cranial haemorrhage, could lead to abnormal loading of the ankle joint and so increased risk.
Neuromuscular conditions present	It is suggested that other concurrent conditions may affect the presentation of haemophilia such as osteoarthritis, cerebral palsy, Charcot-Marie-Tooth or multiple sclerosis.
Age – growth spurts	During a growth spurt, the child's rate of bone growth outstrips the lengthening of muscles and tendons, resulting in what should be temporary alterations such as shortened muscles and weaker ligaments.
Primary hypermobility	Primary generalised congenital hypermobility is associated with increased instability, reduced muscular support and increased risk of inversion sprain making joints less stable and more at risk.
Proprioceptive deficits	Reduced proprioceptive abilities such as decreased feedback/feed forward reaction times (linked to uncontrolled movement), foot placement errors in gait, and reduced balance leading to increased likelihood of injury.
Reduced general fitness	Physical activities may strengthen the muscles to support the joints. It may also improve proprioceptive development thereby providing a protective response against minor injury.

EXTRINSIC FACTORS AFFECTING PHYSICAL HEALTH

Surfaces used for exercise purposes	There is some evidence that exercise surface can affect risk of injury. Uneven surfaces could result in loss of balance. Harder ground could lead to increase stresses on the joint.
Faulty exercise/activity training methods	Overtraining, undertraining or training wrongly for a specific activity.
Footwear choices	Factors such as shock absorption, lack of impact modulation and lack of support within the shoe itself, shoe fashions and not selecting sport-appropriate footwear could adversely affect ankle function.
Growth stage and appropriate activity	A lack of appropriate activity whilst growing could result in reduced development of proprioception and conditioning (general physical fitness). Also poorer functional control during growth spurts as demonstrated by poor muscle control may increase the risk of injury. This may indicate that avoiding sports requiring high levels of motor control may be beneficial.
Lack of protective equipment for chosen activity	Increased risk of trauma without the appropriate equipment for the activity/exercise.
Level/intensity of physical activity	High level activity or highly intensive activity might lead to subclinical bleeding within the weight bearing joints. Also, plainly suggested that those who exercise more sustain more bleeds.
Ankle injury prevalence within the population	It is proposed that the activity levels within the haemophilia population have normalised and the prevalence of ankle disease reflects the fact that the ankle is one of the most commonly injured joints.
Occupational/vocational choices	Jobs requiring heaving lifting or prolonged standing may increase ankle loading and so risk of bleeding.
Physical activity choices	Choosing to play sports with inherent risk of lower limb injury (e.g. football, basketball, scootering, trampolining and ice hockey) will increase overall risk of ankle bleed. Also, increases overall impact loading on the joint.
Repetitive action in daily life	It is suggested that normal low load repetition such as when driving may be enough to overload the ankle joint leading to bleeding.
Unprotected motion in affected joint	In an already affected joint with thickened synovium, normal motion could result in synovial pinching and thereby more bleeding.
Cigarette smoking	It is suggested that smoking is proinflammatory
TREATMENT COMPLIANCE, EDUCATION & NON-HAEMATOLOGICAL MANAGEMENT	
Poor adherence to treatment regimen	Bleeds resulting from not adhering to recommended prophylactic regimen & so circulating factors not high enough to cope with demands.
Poor adherence to rehabilitation programmes	It is proposed that incomplete rehabilitation leads to persistent weakness, altered motor control strategies and a return to activities without being fully fit which may ultimately result in further injuries.
Early effective bleed management	This reflects the education of the patient/carers and includes issues such as recognising a bleed, how soon and how long to continue factor replacement treatment and when to seek advice. Additionally, how long to rest and how much to restrict weightbearing post-bleed.

Growth-appropriate factor regimen	Growing children need adequate cover and this varies. Should there be further cover during growth spurts considering the additional biomechanical stresses that exist that may not be taken into account by the current calculations for treatment dose?
Haemorrhage enhancing medications	The potential of medications for other conditions to directly affect the propensity to bleed.
Global ineffective patient education	Patients showing evidence of a basic lack of understanding of how to manage their condition such as timing their prophylaxis to be most effective at times of day when activity is greatest. Also a generational issue whereby patients born in the era of prophylaxis have not known what it is to experience joint bleeds regularly and so exhibit disbelief or possibly denial about their condition.
Identification and treatment of chronic synovitis	Lack of consensus on how to deal with this clinical sequela which is known to increase the rate of bleeds and subclinical bleeding.
Practitioner not ensuring effective rehabilitation	It is proposed that without full rehabilitation there is a risk of reduced power and proprioception which may result in further injuries. It is also suggested that rehabilitation is neglected where bleeds are less severe.
Lack access to treatment	Due to geographical or financial issues, patients are unable to access either the management advice/support that they require or the actual factor replacement due to local health care systems.
Non-weight bearing during bleed	This was proposed to be a known factor for increasing cartilage damage.
Bleeding before prophylaxis	This represents those who with no family history and therefore are only diagnosed after bleeding has occurred or clinicians accepting minor bleeds into the ankle prior to beginning prophylaxis
HAEMATOLOGICAL FACTORS	
Bleeding before prophylaxis	This represents those who with no family history and therefore are only diagnosed after bleeding has occurred or clinicians accepting minor bleeds into the ankle prior to beginning prophylaxis
Number of bleeds in a joint	It is suggested that this may have a degree of correlation with development of arthropathy. It is suggested that this is the main cause of synovitis and arthropathy.
Levels of factor VIII/IX	This defines the severity of the haemophilia. It is expected that a person with the lowest levels of circulating factor levels will result in an increased rate of bleeding.
Inhibitor formation	This affects the efficacy of the factor replacement regimen and so will result in an increased risk of bleeding.
Genetic propensity to joint damage	Such as autoimmune conditions, altered immune responses, connective tissue diseases and altered inflammatory responses.
Sub-clinical bleeding	There is a suggestion that sub-clinical bleeding occurs more than is realised through normal daily use due to the high load and activity of the ankle joint.

Sufficiency of factor regime	There is a suggestion that early bleeds are not treated aggressively enough. This also represents the suggestion that the current dosing regimens are not adequate for everyone.
Type of factor treatment regimen	It is suggested that using prophylaxis over on-demand regimens will influence the occurrence of bleeding.
Severe bleeding phenotype	It is known that mild haemophiliacs can have significant bleeds and severe haemophiliacs can have few bleeds. It is suggested that this is associated with gene mutations. Additionally, those with more bleeding can have no apparent consequences to their joints and those with minor bleeds can present with far reaching consequences.
ROUND 3 - NEW ADDITIONS	
Specific foot & ankle biomechanics and anatomy	The ankle joint is subject to high stresses and demands. It is suggested that its shape and configuration contribute to this. Also there are many alterations in the ankle/foot posture and motion that could increase risk of bleeding or injury such as rearfoot valgus, over-pronation of the foot in the stance phase of gait or high-arched foot posture.
Weight/BMI	Increased BMI has been linked to the occurrence of ankle sprain and other injuries. It is also linked to increased forces applied to the ankle joint. Also suggested is a higher rate of subclinical bleeds.
Activity levels at younger age	Children are busy. Children prior to formal sit-down teaching spend more of their day at play.
Communication at younger age	Children may be having small bleeds before they can express themselves

Appendix 4. Case-Control Study: Ethical Permission Letters

03/11/2014 – Letter reissued to correct version numbers of non-validated questionnaires and document date of protocol



Health Research Authority

NRES Committee East of England - Hatfield

Rolling Mill Road
Jarrow
Tyne and Wear
NE32 3DT

Telephone: 0191 4283564

24 September 2014 – Reissued 14 October 2014 and 03 November 2014

Miss Ann McCarthy
Research Physiotherapist
Royal Free London NHS Foundation Trust
The KD Haemophilia & Thrombosis Centre
Royal Free London NHS Foundation Trust
London
NW3 2QG

Dear Miss McCarthy

Study title:	Evaluation of the Effect of Musculoskeletal and Exercise Factors on the Development of Joint Disease in Haemophilia.
REC reference:	14/EE/1137
Protocol number:	FREGC-14-035
IRAS project ID:	159597

Thank you for your letter of 18 September 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Miss Kathryn Murray, nrescommittee.eastofengland-hatfield@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the

A Research Ethics Committee established by the Health Research Authority

03/11/2014 – Letter reissued to correct version numbers of non-validated questionnaires and document date of protocol

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Copies of advertisement materials for research participants [advertising poster]	v0.01	17 July 2014
Covering letter on headed paper		26 August 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance doc]	v0.01	18 July 2014
Letter from funder [Pfizer approval letter]		29 August 2014
Letters of invitation to participant [invitation letter]	v0.01	18 August 2014
Non-validated questionnaire [Physical Activity Q_adult Groups 3 & 4]	V0.02	23 June 2014
Non-validated questionnaire [Physical Activity Q_12-17 Groups 3 & 4]	V0.02	23 June 2014
Non-validated questionnaire [Physical Activity Q_adult Groups 1 & 2]	V0.08	23 June 2014
Non-validated questionnaire [Physical Activity Q_12-17 Groups 1 & 2]	V0.05	23 June 2014
Other [PIS participant Group 1]	v0.03	17 July 2014
Other [PIS young person Group 4]	v0.03	17 July 2014
Other [CV academic supervisor]	v0.01	21 August 2014
Other [PIS participant Group 2]	v0.03	17 July 2014
Other [PIS young person Group 3]	v0.03	17 July 2014
Other [CV academic supervisor]	v0.01	19 August 2014
Other [PIS Participant Group 4]	v0.03	17 July 2014
Other [PIS parents group 3]	v0.03	17 July 2014
Other [PIS young person Group 2]	v0.03	17 July 2014
Other [Response cover letter]		18 September 2014
Other [PIS parents Group 4]	v0.03	17 July 2014
Other [PIS young person Group 1]	v0.03	17 July 2014
Other [PIS parent Group 2]	v0.03	17 July 2014
Other [PIS participant Group 3]	v0.03	17 July 2014
Participant consent form [parental consent]	v0.03	18 September 2014
Participant consent form [participant consent form]	v0.01	18 September 2014
Participant consent form [participant consent]	v0.03	18 September 2014
Participant consent form [young person consent]	v0.03	18 September 2014
Participant information sheet (PIS) [PIS parents Group 1]	v0.03	17 July 2014
REC Application Form [REC_Form_29082014]		29 August 2014
Research protocol or project proposal [MSK factors and haemophilic arthropathy]	v12	12 August 2014
Summary CV for Chief Investigator (CI)	v0.01	17 July 2014
Summary CV for supervisor (student research)	v0.02	19 August 2014
Summary, synopsis or diagram (flowchart) of protocol in non	v0.01	19 August 2014

03/11/2014 – Letter reissued to correct version numbers of non-validated questionnaires and document date of protocol

technical language [Overall study flow diagram]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [testing protocol flow chart]	v0.01	21 August 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document “*After ethical review – guidance for researchers*” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

03/11/2014 – Letter reissued to correct version numbers of non-validated questionnaires and document date of protocol

14/EE/1137

Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely



Professor Barry Hunt
Chair

Email: nrescommittee.eastofengland-hatfield@nhs.net

Enclosures: "After ethical review – guidance for researchers" [SL-AR2]

Copy to: Prof Julie Scholes, University of Brighton
Liba Stones, Royal Free London NHS Foundation Trust

Ethics and Governance Committee - Decision on Manuscript ID FREGC-14-035.R1
on behalf of J.Scholes+brighton.ac.uk@manuscriptcentral.com
[on behalf of J.Scholes+brighton.ac.uk@manuscriptcentral.com] on behalf of
J.Scholes@brighton.ac.uk [J.Scholes@brighton.ac.uk]
You replied on 21/08/2014 14:40.
Sent: 21 August 2014 13:00
To: [McCarthy Ann \(ROYAL FREE LONDON NHS FOUNDATION TRUST\)](#)
Cc: a.mandy@brighton.ac.uk
21-Aug-2014

Dear Ms. McCarthy:

It is a pleasure to approve your application entitled "Evaluation of the Effect of Musculoskeletal and Exercise Factors on the Development of Joint Disease in Haemophilia" which has been approved by the Faculty of Health and Social Science Research Ethics and Governance Committee.

Please notify The Chair of FREGC immediately if you experience an adverse incident whilst undertaking the research or if you need to make amendments to the original application.

We shall shortly issue letters of sponsorship and insurance for appropriate external agencies as necessary.

We wish you well with your research. Please remember to send annual updates on the progress of your research or an end of study summary of your research.

Sincerely,
Prof. Julie Scholes
Chair, Faculty of Health and Social Science Research Ethics and Governance Committee
J.Scholes@brighton.ac.uk

Appendix 5. **Case-Control Study: Information Sheet for Adult
Haemophilia Ankle Group**

**University of Brighton
Centre for Clinical Research**

**Evaluating how joint, muscular and exercise factors affect the development of joint disease
in haemophilia.**
Participant Information Sheet for Adults Group 1 Haemophilia with Ankle Problems

1 Study title

Evaluation of the Effect of Musculoskeletal Factors on the Development of Joint Disease in Haemophilia

2 Invitation

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

3 What is the purpose of the study?

In this we are study hoping to find out whether things other than your haemophilia affect how much or how often you bleed into your ankle joint. We have designed a new assessment tool to assist us in determining this which consists of clinical tests and surveys. We are asking you to undergo an assessment to help us determine this.

4 Why have I been invited?

You have been invited to take part in this study because you have a history of bleeding into your ankle joints, but currently it is not troubling greatly in your day to day activities. Unfortunately you will not be able to take part if you have had any major surgery or procedures on your ankle, if any of your other lower limb joints are badly affected by joint disease, and finally if you have any other condition that might affect your balance. Also, should you decide to take part, your visit may be postponed if you have experienced an ankle or knee bleed within 6 weeks of the visit date or if one is present on day of testing.

5 Do I have to take part?

It is up to you to decide; it is totally voluntary. We will describe the study and go through this information sheet, which we will then give to you. Please take it away and decide whether you would like to help us in this research. If you decide to take part, then please read and sign the attached Consent Forms and return one to us in the envelope provided, keeping a copy for your own records. You are free to withdraw at any time, without giving a reason. You will not be affected in any way by a decision not to take part or withdraw.

6 What will happen to me if I take part?

You will be asked to attend a treatment centre on one occasion. You will be asked to answer some questions and also to perform some simple clinical tests. An ankle assessment that you have already experienced as part of your normal care will be repeated followed by a set of clinical tests used to measure aspects of your strength, flexibility, balance and fitness. Depending on how your condition shows itself, you may or may not have done these tests before. For one test, we will video you performing a movement for analysis after the session; these images will be

deleted immediately after grading. The questionnaires will be alternated with the clinical tests to allow you to rest in between. The questions will also be about flexibility and exercise. We expect that this whole process will take no longer than 1.45 hours in total. Depending on your answers to the exercise questionnaire, we may contact you to do a 30 minute follow up interview to make sure we have learned and understood as much as possible. This interview would be recorded. We would also like to look at your medical records to access data about your haemophilia so that we do not have to use your time to ask you. Please inform us if you do not want us to do this.

Whilst we are confident that the clinical tests being used are low risk, we would ask that you ensure that you have used some prophylaxis in order to be doubly sure. We will check your blood pressure and heart rate on the day of testing to make sure you are fit enough to take part. We would also ask that you do not partake of alcohol for 24 hours prior to the study as this may have a residual effect on your ability to balance.

Please bring shorts and trainers with you.

7 What are the possible disadvantages and risks of taking part?

The prophylaxis that you have taken offers some protection against sustaining a bleed. I will ask whether you have used prophylaxis before we begin. If you have not, we may consider re-arranging the appointment. Please inform me immediately during the testing if you should feel any discomfort or are concerned in any way.

8 What are the possible benefits of taking part?

There may not be an immediate benefit to you in taking part in this research, but the information will allow us to improve our understanding of the things that contribute to the development of ankle joint disease in people with haemophilia.

9 What if there is a problem?

*Any complaint about the way you have been dealt with during the study or any possible harm you might have suffered can be addressed by contacting my supervisor, Dr Pratima Chowdary. Alternatively you can contact the Patient Liaison and Advice Service (PALS) on**
For further contact details see the bottom of the information sheet

10 Will my taking part in the study be kept confidential?

The information you provide during the assessment and information about your haemophilia will be entered on an electronic spreadsheet which will be stored on an encrypted NHS computer. You will be referred to by a reference code on the spreadsheet and no personal identifiable information will be stored. Only the researchers will be able to access this information. This information will be kept until the series of studies is completed when it will be destroyed, approximately 3 years. Copies of consent forms, case record forms, and results will be filed in a dedicated study folder and stored in a locked room dedicated for clinical trials and studies.

11 What will happen to the results of the research study?

This study is part of a PhD programme. The results of all the people taking part in the study will be analysed both by statistics and text exploration to see if we can establish any relationships between the things that we tested for and a person with haemophilia's tendency to develop ankle joint disease. The results of this study will also be presented at National and International meetings and in peer-reviewed journals.

12 Who has reviewed the study?

This study has been reviewed and approved by the Faculty of Health and Social Science Research Ethics and Governance Committee, University of Brighton and the NHS Research Ethics Committee (London - Hampstead Area).

13 Contacts for further information

PhD Principal Investigator

Ann McCarthy
Research Physiotherapist
The KD Haemophilia centre & thrombosis unit
Royal Free Hospital
Pond Street NW3 2QG
Tel: 020 7794 0500 ext. 35921
annmccarthy@nhs.net

Co-Principal Investigator (Clinical Supervisor)

Dr Pratima Chowdary
Consultant Haematologist
The KD Haemophilia centre & thrombosis unit
Royal Free Hampstead NHS Trust
London NW3 2QG
Telephone no: 020 7794 0500 ext 35921
p.chowdary@nhs.net

*Individual centres local office numbers will be entered here.

Appendix 7. Case-Control Study: Example Case Record Form

Subject No. 125 Identifier [REDACTED] Site: 1 16.07.2015

PROTOCOL CHECK LIST AID	Tick to indicate each test/survey has been carried out.
Physical Activity Questionnaire	<input checked="" type="checkbox"/>
Height and weight. Measure leg, arm span and foot length	<input checked="" type="checkbox"/>
All things supine: Anterior draw test & subtalar & great toe joint range	<input checked="" type="checkbox"/>
Ankle Lunge Test	<input checked="" type="checkbox"/>
Start Excursion Balance Test	<input checked="" type="checkbox"/>
Foot Posture Index	<input checked="" type="checkbox"/>
Timed Single Leg Stance	<input checked="" type="checkbox"/>
Brighton Criteria, 5-Point Hypermobility & Functional Dyspraxia Questionnaires	<input checked="" type="checkbox"/>
Single Leg Squat Test	<input checked="" type="checkbox"/>
Calf strength test	<input checked="" type="checkbox"/>
Human Activities Profile	<input checked="" type="checkbox"/>
Grip Test	<input checked="" type="checkbox"/>
Tecumseh Step Test	<input checked="" type="checkbox"/>
FAAM/CAIT surveys	<input checked="" type="checkbox"/>

An Exploratory Study for Developing an Assessment Instrument for Evaluation of Non-Haematological Factors and their Effect on the Development of Joint Disease in Haemophilia. Author: A McCarthy
 Version 1.5: 22nd Jul. 2013
 Authorised by: P Chowdary/A Moore/L Redhead

Subject No. 125

Identifier: [REDACTED]

Site: 1

16.07.2015

SCREENING DATA ALL GROUPS

Hospital No.	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Participant ID	1 2 5
Last Name:	[REDACTED]	First Names:	[REDACTED]

Participant Informed Consent:	
Date participant signed written consent form:	Date of assessment:
<i>16.07.2015</i> <small>(DD / MMM / YYYY)</small>	<i>16.07.2015</i> <small>(DD / MMM / YYYY)</small>
Name of person taking informed consent: <i>ANN MCCARTHY</i>	

Demographic Data:				
Date of Birth: [REDACTED] [REDACTED] [REDACTED] <small>(DD / MMM / YYYY)</small>				
Ethnicity:				
White	White British <input checked="" type="checkbox"/>	White Irish <input type="checkbox"/>	White Other <input type="checkbox"/>	
Mixed race	White & Black Caribbean <input type="checkbox"/>	White & Black African <input type="checkbox"/>	White & Asian <input type="checkbox"/>	Other mixed background <input type="checkbox"/>
Asian or Asian British	Indian <input type="checkbox"/>	Bangladeshi <input type="checkbox"/>	Pakistani <input type="checkbox"/>	Other Asian background <input type="checkbox"/>
Black or Black British	Caribbean <input type="checkbox"/>	African <input type="checkbox"/>	Black Other <input type="checkbox"/>	
Chinese or other ethnicity	Chinese <input type="checkbox"/>	Other <input type="checkbox"/> (please specify)		
Gender:	<input checked="" type="checkbox"/> Male		Red hair:	<input type="checkbox"/> Self
				<input checked="" type="checkbox"/> Family <i>- wife</i>

Subject No. 125

Identifier: [redacted]

Site: 1

16, 07, 2015

ELIGIBILITY CHECKLIST – HAEMOPHILIA GROUPS

	Yes	No
ABLE TO STEP UP A 24CM STEP?	Y	
GAIT PATTERN GROSSLY NORMAL?	Y	

HAEMOPHILIA JOINT HEALTH SCORE

If this score is not available in medical records, please complete the scannable score attached at the end. If the score is available, please transfer the results into the scannable document after the participant has left.

Subject No.

125

Identifier:



Site:

1

16, 07, 2015

ELIGIBILITY CHECKLIST – ANKLE GROUPS

	Yes	No
ABLE TO STEP UP A 24CM STEP?		
GAIT PATTERN GROSSLY NORMAL?		

1. Criterion	2. Yes (Y) or No (N)	3. Additional information
How long ago was your first sprain? (years and months), Must be > 12 months ago. Enter in column 3		
Did you need to rest the ankle using crutches or a temporary cast?		
When did you last sprain requiring you to alter your activities or seek treatment? Last sprain must be > 3 months ago. Enter in column 3.		
Number of previous sprains to date. Enter in column 3		
Frequency of sprains. E.g. once per month. Enter in column 3		
Does your ankle "give way" resulting in you turning it without it becoming painful or spraining?		
How often does this occur? E.g. once per month. Enter in column 3		
Do you have the feeling or fear that the ankle is unstable during normal or physical activities?		
How often does this occur? E.g. once per month. Enter in column 3		
Do you get pain in the ankle during daily activities? Y or N		
Any other injuries at time of original sprain? Enter in column 3		
Did the problem begin because of trauma or an accident?		
Did the problem begin slowly?		
Recurrent sprain? Y/N		Perceived instability? Y/N

An Exploratory Study for Developing an Assessment Instrument for Evaluation of Non-Haematological Factors and their Effect on the Development of Joint Disease in Haemophilia.

Author: A McCarthy

Authorised by: P Chowdary/A Moore/L Redhead

Version 1.5: 22nd Jul. 2013

Subject No. 125

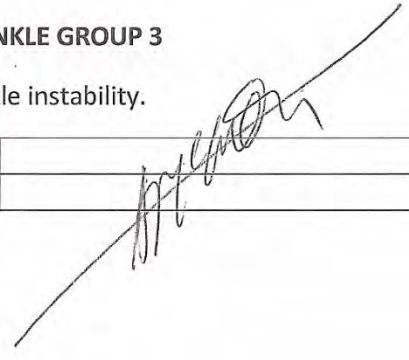
Identifier: [REDACTED]

Site: 1

16, 07, 2015

ELIGIBILITY CHECKLIST – ANKLE GROUP 3

Diagnosis if not chronic ankle instability.

Diagnosis	
Time since diagnosis	

ANKLE JOINT DETAILS

Please tick the appropriate box

	Unaffected	Affected
Left	✓	
Right	✓	

For those with bilateral symptoms, which side is deemed the involved (most affected) side?
Tick appropriate box.

Left

Right

Subject No.

Identifier:

Site: 

PHYSICAL ASSESSMENT DATA

HEIGHT/CM

WEIGHT/KG

BMI

RESTING BLOOD PRESSURE/mmHg

RESTING HEART RATE/BPM

Subject No. 125

Identifier: 12

Site: 1

16.09.2015

PHYSICAL RANGE OF MOTION & STABILITY MEASURES


MEASURES	LEFT	RIGHT	COMMENT
LEG LENGTH/CM	91.9 91.9	92.4	
ANTERIOR DRAW/ Grade 0,1,2,3	1	1	
SUBTALAR INVERSION	42	42	
SUBTALAR EVERSION	16	17	
GREAT TOE DORSIFLEX	25	24	

ANKLE LUNGE TEST

RECORD A NEGATIVE MEASURE TO INDICATE NO WALL CONTACT

LEFT	RIGHT
-147	141
153	147
153	149

Subject No. 125

Identifier: 

Site: 1

16.07.2015

STAR EXCURSION BALANCE TEST

	LEFT	NORMALISED FOR LEG LENGTH*	RIGHT	NORMALISED FOR LEG LENGTH
ANTERIOR 1	.557		.60	
2	.592		.664	
3	.644		.707	
POSTEROMEDIAL 1	.439		.485	
2	.501		.530	
3	.536		.540	
POSTERIOR 1	.538		.638	
2	.540		.64	
2	.575		.742	

*Distance/leg length x 100

Subject No. 125

Identifier: [redacted]

Site: 1

16.07.2015

FOOT POSTURE INDEX

FACTORS	LEFT +2 TO -2	RIGHT +2 TO -2
TALAR HEAD PALPATION	+1	+1
CURVES ABOVE & BELOW LATERAL MALLEOLI	0	+1
INVERSION/EVERSION OF CALCANEUS	+1	+1
PROMINENCE IN THE REGION OF TNJ	+1	0
CONGRUENCE OF MEDIAL LONGITUDINAL ARCH	0	0
ABD/ADDUCTION FOREFOOT ON REARFOOT	0	+1
TOTAL		

Subject No. 125

Identifier: [REDACTED]

Site: 1

[REDACTED] 16.07.2015

TIMED SINGLE LEG STANCE


	LEFT			RIGHT			
TIMED SINGLE LEG STANCE/SECS	27.53	27.97	20.65	6.63	24.35	29.48	EYES OPEN
TIMED SINGLE LEG STANCE/SECS	2.64	3.38	10.12	2.45 3.45	1.44	2.44	EYES CLOSED

BEIGHTON SCORE

	LEFT	RIGHT
ELBOW EXTENSION ≥ 10°	0	0
KNEE EXTENSION ≥ 10°	0	0
THUMB TO WRIST Y/N	0	0
5 TH MCP EXTENSION ≥ 90°	0	0
HANDS TO FLOOR Y/N	0	TOTAL/9 0

NOW PARTICIPANT COMPLETES HYPERMOBILITY/DYSPRAXIA SURVEYS

Subject No. 125

Identifier: 

Site: 1

16.07.2015

SINGLE LEG SQUAT TEST

	LEFT	RIGHT	
SINGLE LEG SQUAT/poor-fair-good	Fair	Fair	

CALF STRENGTH

	LEFT	RIGHT	
CALF STRENGTH/REPS	20	19	

NOW PARTICIPANT COMPLETES THE HAP SURVEY

Subject No. 125

Identifier: [REDACTED]

Site: 1

16.07.2015

GRIP TEST

	LEFT	RIGHT
1	41.6	47.2
2	43.9	47.6

TECUMSEH STEP TEST

FIT FOR STEP TEST? YES OR NO.	Y
HEART BEATS 30 SECS TO 1 MIN.	38

NOW PARTICIPANT COMPLETES THE FAAM/CAIT SURVEYS

PARTICIPANT MAY LEAVE

Appendix 8. Case-Control Study: Exploratory Activity Questionnaire

Physical Activity Survey
(Occupation, Sport and Activity)

Date: 16/07/15
Participant No.: 125/ [redacted]

Thank you for taking part in the survey. We are interested in knowing about how active you are now and, if possible, in the past related to both your occupation and any physical activity, formal or informal. There are also some questions about injury and recovery. Please answer as much as you can.

Section A. These questions are about your education and occupation. If you are not working, please try to fill in questions 4 & 5 thinking about your every day life instead.

1, At what age did you finish your formal education?

- Left school under 16
- Between 16 - 17
- Between 18 - 20
- Aged 21 or over
- I'm still studying

2, Please list all your occupations since leaving school. How long did they last?

JOB	YEARS	MONTHS
E.g. Shop assistant	0	9
- Research Technician (active)	3	0
- Field sampler (active)	1	0
- Office jobs (operations)	4	
- Project manager (office)	1	0
- Network investigator (active)	1	0
- Project Manager (office/active)	10	0
- Delivery Manager (office)	2	0

1 Author: Ann McCarthy
Authorised by: Ann Moore, Pratima Chowdary & Lucy Redhead
Version: 0.08 Date: 23/06/2014

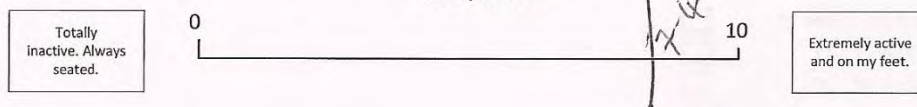
Physical Activity Survey (Occupation, Sport and Activity)

3, If you are currently not working, is this due to haemophilia-related issues?

Yes No Not applicable Other - please specify

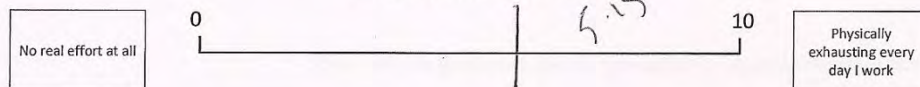
4,

How active do you consider you have been in your main or longest lasting occupation?



5,

How much physical effort or energy has been needed to carry out your main or longest lasting occupation?



SECTION B. These questions are about exercise and physical activity.

6. If you have **never taken part in any** regular exercise at all please could you tell us why?

Exercise and activities could include gym, walking more than 15 minutes, table tennis, volleyball, jogging, dancing, climbing, fencing, hiking, races in P.E. classes, paper round, go-karting. **PLEASE INCLUDE PLAYGROUND/PLAYING OUT PHYSICAL ACTIVITIES.**

N/A

If you have filled in question 6 you have now finished the survey. – Thank you!

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Author: Ann McCarthy

Authorised by: Ann Moore, Pratima Chowdary & Lucy Redhead

Version: 0.08

Date: 23/06/2014

Physical Activity Survey (Occupation, Sport and Activity)

7. Please list any sports or other physical activities you have participated in regularly including informal games with friends and playground games. Also include daily activities such as walking. Please **tick** the boxes to indicate how old you were for each sport/activity and how many years you took part.

Activities ↓	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
E.g. Playground football						✓	✓	✓	✓	✓	✓	✓	✓																	
Football - primary					✓	✓	✓	✓	✓	✓	✓	✓	✓																	
Football - S-side																														
Cricket																														
Swimming																														
Hiking																														
walking																														
P.E. classes																														
Cycling																														
Squash																														
Activities ↓	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Age →																														
Football - S-side																														
Cricket																														
Swimming																														
Hiking																														
walking																														
Cycling																														

Activities could include: gym, walking more than 15 minutes, table tennis, volleyball, jogging, dancing, climbing, fencing, hiking, races in P.E. classes, paper round, go-karting. **PLEASE INCLUDE PLAYGROUND/PLAYING OUT PHYSICAL ACTIVITIES.**

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Version: 0.08 Date: 23/06/2014

Physical Activity Survey
(Occupation, Sport and Activity)

8. For the 5 physical activities that you've spent most time doing, please can you answer the following questions. Feel free to ask the researcher questions.

Activity	How often did or do you take part?	Where did you take part? (school, club, park, gym, playground)	At what level did you take part? (casual, regular amateur, competitive amateur)	Did you ever have any injury due to the sport? (Yes or no)	If you had an injury, why do you think it happened? (Training error, collision with player, over did it etc)
1 Walking	daily	everywhere	casual	Yes	Over exertion
2 Swimming	monthly	local pool/holiday	casual	Yes	Over exertion
3 Football 5 a side	monthly	local sports centre	Casual	Yes	Over exertion
4 Badminton	annually	holiday	Casual	Yes	Over exertion
5 Cycling	daily	roads	Casual	Yes	Over exertion

4 Author: Ann McCarthy

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Version: 0.08 Date: 23/06/2014

Physical Activity Survey (Occupation, Sport and Activity)

9, Thinking about the activity or sport that you have done the most. How did you learn how to do it?
Please tick all that apply.

- Just did it
- Through magazines
- On-line/websites
- Sports at school
- Advice from friends
- Advice from haemophilia treatment centre
- Semi-professional trainer, coach or teacher
- Professional trainer or coach
- Other, please specify in the box below

11, Please tick all the exercise/training/activity surfaces that you have used.

- | | | |
|--|---|---|
| Grass (level playing field) <input checked="" type="checkbox"/> | Grass (uneven) <input type="checkbox"/> | Dry slope <input checked="" type="checkbox"/> |
| Paving (tarmac/concrete/stone) <input checked="" type="checkbox"/> | Ice/snow <input type="checkbox"/> | Astroturf <input checked="" type="checkbox"/> |
| Other uneven surfaces <input checked="" type="checkbox"/> | Sprung flooring <input checked="" type="checkbox"/> | None <input type="checkbox"/> |
| Rubberised track <input checked="" type="checkbox"/> | Wooden floors <input checked="" type="checkbox"/> | |
| Ash courts <input checked="" type="checkbox"/> | Water <input checked="" type="checkbox"/> | |

12, Did your main exercise require protective equipment such as shin guards?

- Yes
- No If "no", go to Q 14.

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Version: 0.08 Date: 23/06/2014

Physical Activity Survey (Occupation, Sport and Activity)

13, How often do you or did you wear the protective equipment required by your chosen sport/activity?

Never 0 10 Always

14, Do you ever have minor injuries to your joints that you don't mention to anyone such as minor sprains?

Yes
No

15, Please would you tell us why you didn't tell anyone?

temporary, no need to mention
severity - low

16,

When you tell your support team about a bleed or injury, are you offered rehabilitation, exercises or stretches?

Never 0 10 Always

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Version: 0.08

Date: 23/06/2014

**Physical Activity Survey
(Occupation, Sport and Activity)**

17,

How well do you stick to instructions when you are given exercises or stretches to do at home by your clinical support team?

Never 0 4.6 10 Always

18, If you have ever failed to carry out exercises suggested to you by your haemophilia centre, would you please tell us why? It can be just a single word answer.

blake - when injury generally less severe, low adherence to instructions. More notice of instructions for serious injuries

19, As a child, do you remember playing the same games as your friends?

Yes (mostly)
No
Don't remember
Don't know

20, Were there certain games that you weren't allowed to play?

Yes If, yes - please write what they were in the box below.
No
Don't remember

Rugby, Competitive 11 a side football,

Physical Activity Survey (Occupation, Sport and Activity)

21. How did you get to take part in your sports and physical activities? You can tick more than one box.

- My parents picked them for me
- My parents and doctors/nurses/physio picked them
- My doctors/nurses and physios picked them
- I was involved in deciding with others
- There were things that my school didn't allow me to do
- I chose what I wanted to do

22. Overall, do you feel that you ran around more, the same or less than your friends when you were 5 years old?

- Same
- More
- Less
- Can't remember

23. And at 10 years old?

- Same
- More
- Less
- Can't remember

24. And at 15 years old?

- Same
- More
- Less
- Can't remember

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Author: Ann McCarthy

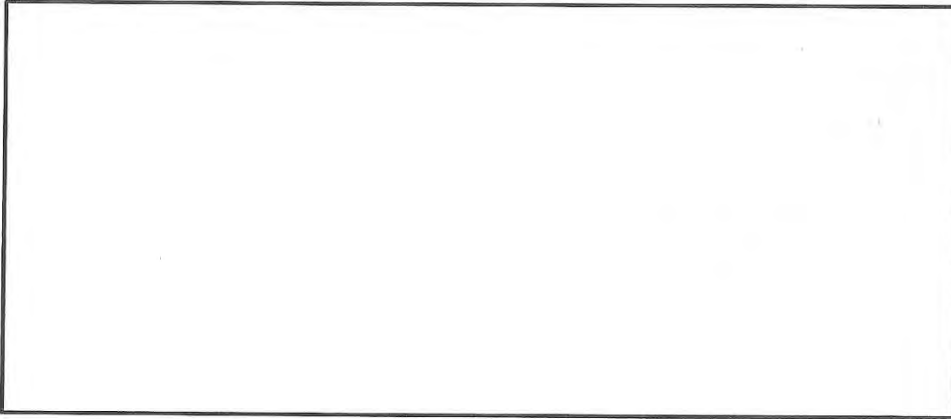
Authorised by: Ann Moore, Pratima Chowdary & Lucy Redhead

Version: 0.08

Date: 23/06/2014

**Physical Activity Survey
(Occupation, Sport and Activity)**

25. Is there anything else about occupation, sport and exercise that you think might be important to how haemophilia affects you that we haven't asked?



Heptatitis - affected energy levels. Aged 40.

Thank you very much for completing this survey!

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Author: Ann McCarthy

Authorised by: Ann Moore, Pratima Chowdary & Lucy Redhead

Version: 0.08 Date: 23/06/2014

Appendix 9. Case-Control Study: Hypermobility Questionnaires

Participant Completed Questionnaire 2

ID 1,2,5

A. Place a tick in the box that applies to you

- | | Yes | No |
|---|--------------------------|-------------------------------------|
| 1. Can you now (or could you ever) place your hands flat on the floor without bending your knees? | <input type="checkbox"/> | <input checked="" type="checkbox"/> |
| 2. Can you now (or could you ever) bend your thumb to touch your forearm? | <input type="checkbox"/> | <input checked="" type="checkbox"/> |
| 3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits? | <input type="checkbox"/> | <input checked="" type="checkbox"/> |
| 4. Do you consider yourself to be double-jointed? | <input type="checkbox"/> | <input checked="" type="checkbox"/> |

B. Please put a tick or cross in the area of the body where you have had pain lasting more than 3 months

	Left	Right
Shoulder	<input type="checkbox"/>	<input type="checkbox"/>
Lower Back	<input type="checkbox"/>	<input type="checkbox"/>
Elbow	<input type="checkbox"/>	<input type="checkbox"/>
Wrist or Hand	<input type="checkbox"/>	<input type="checkbox"/>
Hip	<input type="checkbox"/>	<input type="checkbox"/>
Knee	<input type="checkbox"/>	<input type="checkbox"/>
Ankle	<input type="checkbox"/>	<input type="checkbox"/>
Foot	<input type="checkbox"/>	<input type="checkbox"/>
Neck	<input type="checkbox"/>	<input type="checkbox"/>
Upper Back	<input type="checkbox"/>	<input type="checkbox"/>

Have you ever dislocated any of the following joints? (Put a tick or cross in the appropriate box)

	Yes	No	More Than Once
Shoulder	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Knee	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Finger	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>



Have you ever suffered from any of the following? (Put a tick or cross in the appropriate box)

	Yes	No	More Than Once
Tennis elbow	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Rectal prolapse	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Golfer's elbow	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Frozen shoulder	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Carpal tunnel syndrome	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Achilles tendinitis or tear	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
hernias	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Varicose veins	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

	Yes	No	Not Sure
Do you think you have much longer arms or legs than your friends or colleagues?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Can you wrap your thumb and little finger around your wrist with an overlap?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Do you scar easily	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Do you have stretch marks?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Do you have drooping eyelids?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Have you ever required glasses to correct your vision for seeing into the distance?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

For official use only

Yes	No
<input type="checkbox"/>	<input checked="" type="checkbox"/>



C. Place a tick in the box that applies to you

	Very Good	Good	Poor	Very Poor
AS A CHILD, how good was your handwriting?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
AS A CHILD, how good were you at team games that involved balls? e.g. football, netball, basketball	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
AS A CHILD, how did others rate your coordination?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
AS AN ADULT, how good are you at avoiding obstacles, like bumping into doors?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
AS AN ADULT, how good are you at organising yourself? e.g. getting ready for work or for a meeting	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
AS AN ADULT, how good are you at catching a ball one handed?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
AS AN ADULT, how good are you at balancing on a bike, on a bus or train or on skis?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
AS AN ADULT, how good are you at using your hands e.g. to do jobs around the home, DIY, sewing or using scissors	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
AS AN ADULT, how good is your handwriting?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>



Appendix 10. Case-Control Study: Human Activity Profile

Participant Completed Questionnaire 3

ID 1,2,5

This profile is designed to give an indication of your overall fitness level. For each of the items in the list below, please indicate if you are still doing them, stopped doing them or have never done them by ticking the appropriate box. This should take between 5 and 7 minutes to complete.

	Still Doing	Stopped Doing	Never Did
1. Getting in/out of bed/chairs without assistance	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Listening to the radio	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Reading books, newspapers or magazines	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Writing (letters, notes)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Working at a desk or table	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Standing for more than 1 minute	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Standing for more than 5 minutes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Dressing or undressing (without assistance)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Getting clothes from drawers or wardrobes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Getting in/out of a car (no assistance)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Eating out at a restaurant	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Playing cards/ table games	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
13. Taking a bath (no assistance)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Putting on shoes/socks (no assistance)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Attending cinema, play, sporting or religious event	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Walking approximately 30m/30secs at average pace	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Walking approximately 30m/30secs at average pace non-stop	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Dressing or undressing (no rest or break needed)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
19. Using public transport or drive a car (99miles/156km or less)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
20. Using public transport or drive a car (100miles/160km or more)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
21. Cooking your own meals	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
22. Washing or drying your own clothes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
23. Putting groceries on shelves	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



	Still Doing	Stopped Doing	Never Did
24. Ironing/folding clothes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
25. Dusting/polishing furniture or polishing a car	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
26. Showering	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
27. Climbing 6 steps	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
28. Climbing 6 steps (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
29. Climbing 9 steps	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
30. Climbing 12 steps	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
31. Walking half a block (80m or 1 min) on level ground	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
32. Walking half a block (80m or 1 min) on level ground (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
33. Making a bed (not changing sheets)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
34. Cleaning windows	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
35. Kneeling/squatting to do light work	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
36. Carrying a light load of groceries	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
37. Climbing 9 steps (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
38. Climbing 12 steps (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
39. Walking half a block (80m or 1 min) uphill	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
40. Walking half a block (80m or 1 min) uphill (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
41. Shopping (by yourself)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
42. Washing clothes by yourself	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
43. Walking 1 block (160m or 2 mins) on level ground	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
44. Walking 2 blocks (360m or 4.5mins) on level ground	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
45. Walking 1 block (160m or 2mins) on level ground (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
46. Walking 2 blocks (360m or 4.5mins) on level ground (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
47. Scrubbing (floors, walls or cars)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
48. Sweeping	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



	Still Doing	Stopped Doing	Never Did
49. Making a bed including a sheet change	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
50. Sweeping (5mins non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
51. Carrying a large suitcase or bowling (10 pin) 1 game	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
52. Vacuuming the carpet	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
53. Vacuuming the carpet 5mins (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
54. Painting (interior/exterior)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
55. Walking 6 blocks (960m or 11.5mins) on level ground	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
54. Walking 6 blocks (960m or 11.5mins) level ground (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
57. Carrying out the rubbish/garbage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
58. Carrying a heavy load of groceries	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
59. Climbing 24 steps (2 household flights)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
60. Climbing 36 steps (3 household flights)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
61. Climbing 24 steps (non-stop 2 household flights)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
62. Climbing 36 steps (non-stop 3 household flights)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
63. Walking 1 mile/1.6km/20mins	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
64. Walking 1 mile/1.6km/20mins (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
65. Running 100m or playing rounders/baseball	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
66. Dancing (social)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
67. Doing aerobics or dancing enough to get sweaty (5mins)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
68. Mowing the lawn (not a sit on mower)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
69. Walking 2 miles/3.2km/40mins	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
70. Walking 2 miles/3.2km/40mins (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
71. Climbing 50 steps or 2.5 floors	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
72. Shovelling or digging	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



	Still Doing	Stopped Doing	Never Did
73. Shovelling or digging (5mins non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
74. Climbing 50 steps (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
75. Walking 3 miles/4.8km/1hour or golfing 18 holes no buggy	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
76. Walking 3 miles/4.8km/1 hour non-stop	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
77. Swimming approximately 25m	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
78. Swimming approximately 25m (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
79. Bicycling 1 mile/1.6km/20 mins	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
80. Bicycling 2 miles/3.6km/40 mins	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
81. Bicycling 1 mile/1.6km/20mins (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
82. Bicycling 2 miles/3.6km/40mins (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
83. Running or jogging 0.25 mile/0.5km	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
84. Running or jogging 0.5 mile/0.8km	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
85. Playing tennis or squash	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
86. Playing basketball/football	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
87. Running or jogging 0.25mile/0.5km/3mins (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
88. Running or jogging 0.5mile/0.8km/5mins (non-stop)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
89. Running or jogging 1mile/1.6km/4 laps of a track	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
90. Running or jogging 2 miles/3.6km/8 laps of a track	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
91. Running or jogging 3miles/4.8km/12 laps of a track	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
92. Running or jogging 1mile/1.6km in 12mins or less	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
93. Running or jogging for 20mins or less	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
94. Running or jogging for 30mins or less	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



2 999379 350374

Appendix 11. Case-Control Study: Cumberland Ankle Instability Tool

Participant Completed Questionnaire 4

ID 1,2,5

Please tick ONE statement in EACH question that BEST describes your ankles

1. I have pain in my ankle

	Left	Right	Official Use Only
Never	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
During sport	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Running on uneven surfaces	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Running on level surfaces	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking on uneven surfaces	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking on level surface	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

2. My ankle feels UNSTABLE

	Left	Right	Official Use Only
Never	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Sometimes during sport (not every time)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frequently during sport (every time)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Sometimes during daily activity	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Frequently during daily activity	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. When I make SHARP turns, my ankle feels UNSTABLE

	Left	Right	Official Use Only
Never	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Sometimes when running	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Often when running	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
When walking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



4. When going down stairs, my ankle feels UNSTABLE

	Left	Right
Never	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
If I go fast	<input type="checkbox"/>	<input type="checkbox"/>
Occasionally	<input type="checkbox"/>	<input type="checkbox"/>
Always	<input type="checkbox"/>	<input type="checkbox"/>

Official Use Only

5. My ankle feels UNSTABLE when standing on one leg

	Left	Right
Never	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
On the ball of my foot	<input type="checkbox"/>	<input type="checkbox"/>
With my foot flat	<input type="checkbox"/>	<input type="checkbox"/>

Official Use Only

6. My ankle feels UNSTABLE when

	Left	Right
Never	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
I hop from side to side	<input type="checkbox"/>	<input type="checkbox"/>
I hop on the spot	<input type="checkbox"/>	<input type="checkbox"/>
I jump	<input type="checkbox"/>	<input type="checkbox"/>

Official Use Only

7. My ankle feels UNSTABLE when

	Left	Right
Never	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
I run on uneven surfaces	<input type="checkbox"/>	<input type="checkbox"/>
I jog on uneven surfaces	<input type="checkbox"/>	<input type="checkbox"/>
I walk on uneven surfaces	<input type="checkbox"/>	<input type="checkbox"/>
I walk on flat surfaces	<input type="checkbox"/>	<input type="checkbox"/>

Official Use Only



8. TYPICALLY, when I start to roll over (or "twist") on my ankle, I can stop it

	Left	Right	Official Use Only
Immediately	<input type="checkbox"/>	<input type="checkbox"/>	
Often	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
Sometimes	<input type="checkbox"/>	<input type="checkbox"/>	
Never	<input type="checkbox"/>	<input type="checkbox"/>	
I have never rolled over on my ankle	<input type="checkbox"/>	<input type="checkbox"/>	

9. After a TYPICAL incident of my ankle rolling over, my ankle returns to "normal"

	Left	Right	Official Use Only
Almost immediately	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
Less than one day	<input type="checkbox"/>	<input type="checkbox"/>	
1-2 days	<input type="checkbox"/>	<input type="checkbox"/>	
More than 2 days	<input type="checkbox"/>	<input type="checkbox"/>	
I have never rolled over on my ankle	<input type="checkbox"/>	<input type="checkbox"/>	



Appendix 12. Case-Control Study: Foot & Ankle Ability Measure

Participant Completed Questionnaire 5

ID 1,2,5

Activities of daily living subscale.

Please answer **EVERY** question with **ONE** response that most closely describes your condition within the past week.
If the activity in question is limited by something other than your foot or ankle mark not applicable (N/A).

1. Because of your foot and ankle how much difficulty do you have with:

	No Difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Standing	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking on even ground	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking on even ground without shoes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking up hills	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking down hills	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Going up stairs	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Going down stairs	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking on uneven ground	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Stepping up and down curbs	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Squatting	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Coming up on your toes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking initially	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking 5 minutes or less	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking approximately 10 minutes	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Walking 15 minutes or greater	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



Participant Completed Questionnaire 5

ID 1,25

2. Because of your foot and ankle, how much difficulty do you have with:

	No Difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Home responsibilities	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Activities of daily living	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Personal care	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Light to moderate (standing, walking)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Heavy work (push/pulling, climbing, carrying)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Recreational activities	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

3. How would you rate your current level of function during your usual activities of daily living from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities?

Out of 100 or % 100



Appendix 13. **Glossary of Statistical Procedures used throughout the research programme.**

The purpose of this appendix is to provide an explanation for the selection of statistical tests used throughout the thesis. In addition at the end a worked example is shown for the management of data received in the case-control study.

The purpose of each test is briefly described delineated by the relevant study. Prior to this normality testing procedures for continuous data sets are touched upon.

Assessing the distribution of data points

The majority of data analysis for this research programme was undertaken using SPSS. Assessing for normal distribution within this provides a multitude of output including statistical tests and graphical displays. It is suggested that using a combination of these is the most appropriate way of determining distribution patterns (Laerd Statistics, 2015e). It has been suggested that although the statistical test, usually Shapiro-Wilks test, gives an objective indication of normality, it may overly sensitive to smaller or larger sample sizes (Laerd Statistics, 2015e). Additionally it does not provide an indication of any pattern that your data is following such as skewed or kurtosed and therefore the addition of graphical assessment is recommended. Graphical presentations that can help interpret data include histograms, boxplots and Q-Q plots. It has been suggested that these may be more appropriate methods despite lacking in objectivity (Laerd Statistics, 2015e). For the purposes of this thesis, the researcher determined that determination of normality would be based on the assessment of two out of three tests.

Where the data was not normally distributed, raw data was examined for obvious outliers which then were adjusted to a level of just greater than the data point next down. Normality testing was then repeated. If this did not succeed in correcting distribution then the following data transformations were attempted in order of least to most drastic: square root was taken; logarithm was taken; and finally the inverse was taken (Laerd Statistics, 2015f). If none of these had the required result, non-parametric testing was undertaken. It should be noted that some of the continuous data sets were not normally distributed by virtue of natural design such as the percentage scale for the Foot and Ankle Ability Measure where normal scores are near 100%. In this case the data was adjusted to create a standardised variable by applying the following calculation:

$$Z_i = e_i - \bar{e} / s_e$$

Where Z_i is the standardised variable, e is the original variable, \bar{e} is the mean, s_e is the standard deviation (DeCoster, 2001). Normality testing was then applied.

Study: Preliminary testing of the Star Excursion Balance Test

SEMG analysis was used to assess activity from two muscles over eight different movement directions. The purpose was to ascertain if particular directions generated greater muscle activity. Additionally, analysis was undertaken to determine if these differences were significant between movement directions for each muscle. The following statistical procedures were undertaken:

- *Shapiro-Wilk test* and boxplots indicated that the distribution was not normal.

- *Friedman test* is selected as a non-parametric alternative to the repeated measures analysis of variance (ANOVA) as the testing method included taking three measures for each movement direction where the assumption of normality is violated (Friedman, 1940). This gives an indication of significance across the data set but not where specific differences lie in the eight movement directions.
- *Wilcoxon signed-rank test* is a paired-difference test used to compare the related test samples in a pairwise manner (Wilcoxon, 1945) in order to identify where specific differences lay.
- *Bonferroni correction* is applied in statistics to account for the presence of multiple hypotheses (comparison between the eight movement directions). As the number of hypotheses increases, so does the likelihood of a rare event and consequently increased likelihood of rejecting a null hypothesis. The statistical significance level is reduced by $1/m$ where m is the number of hypotheses (Bender235, 2016).

Study: Evaluation of the Effect of Musculoskeletal and Exercise Factors on the Development of Joint Disease in Haemophilia

Data analysis in this study was complicated by the differing types of data (continuous, ordinal and categorical) and the need to ascertain differences between groups and then degree of influence. The choice and use of logistic regression is fully described in Section 10.6 and so will not be included here. Data was analysed according to assessment of normality distribution as described above. The following tests were utilised depending on results:

- *One-way-ANOVA* is used with continuous data sets to determine if there are differences between the means of two or more independent groups. It is referred to as an omnibus statistic in that it cannot provide detail of between groups differences merely whether they are presence or absent. Post hoc pairwise testing is required to determine where exact differences lie. Some authors suggest that the ANOVA is not required and that the post hoc test is all that is required. The Tukey test is most commonly applied and is described below. Along with a normal distribution, another assumption with ANOVA is the presence of homogeneity of variances (i.e., the variance is equal in each independent variable group). This is tested for automatically in SPSS using the Levene's test of equality of variances (Laerd Statistics, 2015b). If the data fails this assumption then a modified ANOVA is required, described next.
- *Welch's ANOVA* is used when the homogeneity of variances is violated and modifies the ANOVA by performing the procedure with separate variances as opposed to merged variances as occurs in a standard ANOVA. The degrees-of-freedom is also modified. Additionally an adapted post hoc test is used, the Games-Howell, described below (Laerd Statistics, 2015b).
- *Tukey test* is used to perform pairwise comparisons when you have no a priori hypotheses about where differences will lie and want to assess all combinations. This test is recommended where all the ANOVA assumptions are met and it also provides confidence intervals (Kirk, 2013).
- *Games-Howell test* is used for the same purpose as Tukey but where the homogeneity of variances assumption is violated. It also provides

confidence intervals for the differences between group means (Laerd Statistics, 2015b).

- *Kruskal-Wallis test* is a non-parametric version of the one-way-ANOVA. It determines whether there are statistically significant differences present between two or more groups using ranks where there is a continuous or ordinal dependent variable. This again is an omnibus statistic and the Dunne test is used to identify which group is different from which other.
- *Dunn's test* (Dunn, 1964) is applied with a Bonferroni correction (see above) in order to identify specific differences between groups.
- *Receiver operator characteristic (ROC) curve analysis* is performed in diagnostic healthcare to determine whether a given test, scale or screening tool has the ability to discriminate between people definitely presenting with a condition and those who are not. For this study, this was used to identify a score below which membership of the haemophilia ankle group was likely.
- *Mann-Whitney U-test* is used prior to carrying out ROC analysis to ensure that a marked difference exists between the scores of the two groups using continuous or ordinal data.
- *Chi Square test of association* was used where nominal or ordinal (treated as nominal) data was present to determine whether variables are associated or independent from each other. However it does not distinguish between dependent and independent variable but the study design here makes that call (Laerd Statistics, 2015a).
- *Pearson's (parametric) or Spearman's (non-parametric) Correlations* were used to identify any close associations between items going forward for

potential inclusion in the logistic regression procedures. The Pearson correlation determines the strength and direction of a linear association between two continuous variables. A correlation coefficient is produced (r) ranging from -1 to + 1 (Laerd Statistics, 2015c). Whereas Spearman correlation produces the same where data are related in a monotonic way. The correlation coefficient is denoted by r_s or ρ (rho). Continuous or ordinal data may be assessed with Spearman's correlation (Laerd Statistics, 2015d).

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Appendix 14. **Case-Control Study: Tecumseh Step Test Grading**

Montoye et al. (1969) carried out submaximal aerobic testing on the population of a small Canadian town encompassing a population of 2696 males from ages 10 to 69. The step test requires the operator to record the participant’s heart beat for 30 seconds, 30 seconds after ceasing the three minute test. Results are usually presented graded from poor to outstanding in six gradations. These are shown in the table below for ages relevant to this study.

Appendix Table 1. Tecumseh step test grading results

↓ Grade Age →	12 – 13	14 – 15	16 – 17	18 – 19	20 – 29	30 -39	40 - 49
Outstanding	33 – 36	30 – 33	31 – 34	30 - 33	34 – 36	35 – 38	37 – 39
Very good	37 – 39	34 – 38	35 – 38	34 – 38	37 – 40	39 – 41	40 – 42
Good	40 – 41	39 – 40	39 – 40	39 – 41	41 – 42	42 – 43	43 – 44
Fair	42 – 44	41 – 42	41 – 43	42 – 45	43 – 47	44 – 47	45 – 49
Low	45 – 50	43 – 46	44 – 49	46 – 50	48 – 51	48 – 51	50 – 53
Poor	51 - 56	47 - 52	50 - 57	51 - 58	52 - 59	52 - 59	54 - 60

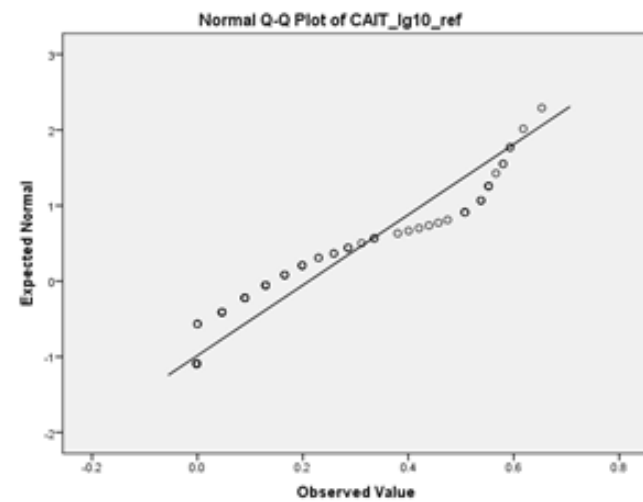
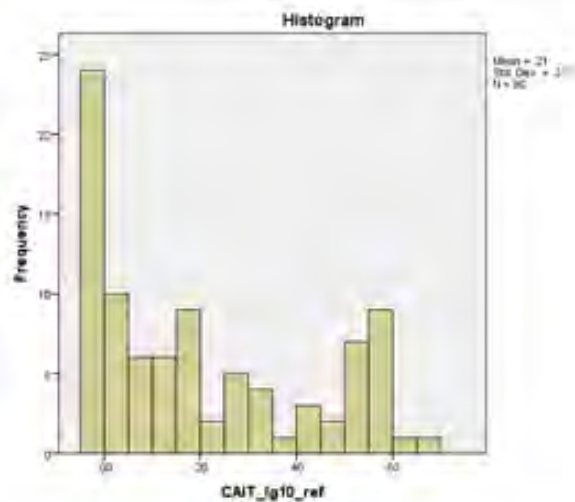
Montoye, H. J., Willis III, P. W., Cunningham, D. A., & Keller, J. B. (1969). Heart rate response to a modified Harvard step test: males and females, age 10–69. *Research Quarterly. American Association for Health, Physical Education and Recreation*, 40(1), 153-162.

Appendix 15. Case-control study: Worked example of data analysis using the Cumberland Ankle Instability Tool (CAIT).

4 cycles of Normality Testing using Shapiro-Wilks, histogram, Q-Q plot and boxplots. The following data transformations and manipulations were carried out:

- creation of standardised variable
- outliers addressed & reflected square root applied
- reflected logarithm applied

After 4th round, 3 out of 3 tests persisted in showing data not normally distributed. Graphs below show histogram and Q-Q plot for the 1st round.

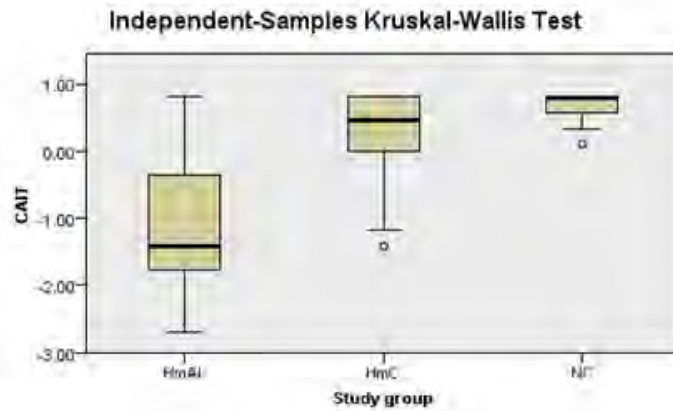


Non-parametric testing - Kruskal Wallis with Dunn post hoc testing carried out. Test results are given in the next box. Graphs below show test result and distributions across groups.

Hypothesis Test Summary

Null Hypothesis	Test	Sig.	Decision
The distribution of CAIT is the same across categories of Study group.	Independent-Samples Kruskal-Wallis Test	.000	Reject the null hypothesis

Asymptotic significances are displayed. The significance level is .05.



Pairwise Comparisons of Study group



Each node shows the sample average rank of Study group.

Sample1-Sample2	Test Statistic	Std. Error	Std. Test Statistic	Sig.	Adj.Sig.
HmAk-HmC	-29.933	6.676	-4.484	.000	.000
HmAk-NC	-42.817	6.676	-6.414	.000	.000
HmC-NC	-12.883	6.676	-1.930	.054	.161

Each row tests the null hypothesis that the Sample 1 and Sample 2 distributions are the same. Asymptotic significances (2-sided tests) are displayed. The significance level is .05.

$\chi^2(2)=43.311$ $p=.0005$. Post hoc testing showed that the distributions of medians was not similar for all groups (see chart above right) and so results are presented for mean ranks. Significant differences were noted between the HmAk (21.25) and HmC (51.18) $p=.0005$ and HmAk and NV (64.07) $p=.0005$.

Data set selected for potential regression analysis. Domain identified and relevance to study assessed.

Multiple Spearman's correlations carried out to assess association with other potential regression items. Found to be closely related to the FAAM**. CAIT discarded as FAAM sport subscale selected for its greater clinical utility.

Appendix 16. Case-Control Study: Full List of Reported Activities

Activity	Count	Activity	Count
5-A-Side Football	2	Orienteering/Cadet Training/Cross Country Running	2
Alpine Skiing	1	Outdoor/Scouting Activities	2
Athletics/Track & Field	4	Paper Round	1
Badminton	5	PE Classes	17
baseball	1	Personal Trainer	1
Basketball	7	Physical Theatre	1
Break Dancing	1	Playground Football	5
Climbing	2	Playground Games	4
Climbing trees	1	Pool/Billiards/Snooker	2
Cricket	12	Riding	1
Cycling	25	Rollerblading	1
Dodgeball	1	Rowing	8
Dog Walking	2	Rugby	4
Domestic Activity	1	Running	29
Football	45	Skateboarding/Longboarding	1
Gaelic Football	1	Snowboarding	1
Gardening	1	Squash	7
Golf	6	Surfing	1
gym	3	Swimming	34
Gym Various/Personal Fitness	26	Table Tennis	3
Gymnastics	2	Tai Chi	1
Hiking	3	Tennis	18
Hockey	2	Touch rugby	1
Hurling	2	trampoline	1
Jogging	3	Triathlon	2
Karate	1	Volleyball	1
Kick Boxing/Thai Boxing/Muay Thai	2	Walking	43
Live Action Role Playing	1	Weight Training	4
Martial Arts	1	Yoga	2
Grand Total			362

Appendix 17. **Case-Control Study: Ankle Risk Coding for Activities**

Activities and sports reported by participants as part of the exploratory activity questionnaire were classified according to the risk of injury to the ankle. This was undertaken as current risk stratification in use with PWH is focussed on the likelihood of catastrophic injury and may underestimate the potential of an activity to impact on arthropathy development at the ankle.

Injury risk data were sourced from published materials, web-based resources such as the U.S. Consumer Product Safety Commission which has a national injury surveillance system, and where published data was unavailable, the researcher used their expert analysis of the load on and usage of the ankle within a given activity.

Table A17 Presenting the activities grouped according to risk with supporting references

	Activity
Low risk	Badminton (0.68 ^a) (Fahlström, 2009; Fong, Hong, Chan, Yung, & Chan, 2007)
	Baseball (0.14 ^c) (Fong, et al., 2007)
	BMX ^e (Dettori & Norvell, 2006)
	Boxing (3.7% ^d) (Zazryn & McCrory, 2009)
	Break dancing ^e (Requa, DeAvilla, & Garrick, 1993)
	Cycling ^e (Pruitt & Carver, 2009)
	Dog Walking ^e
	Domestic Activity ^e
	Gardening ^e
	Golf ^e (Batt, 1992)
	Gym various/personal fitness ^e (Requa, et al., 1993)
	Hiking ^e
	Ice Hockey (0.20 ^a) (Fong, et al., 2007)
	Jogging/running flat (0.02 ^a)
	Orienteering/cadet training/cross country running (0.82 ^a) Orienteering (C 3.8 ^a)
	Outdoor/ Scouting Activities ^e
	Paper Round ^e
	Pilates ^e
	Pool/Billiards/Snooker ^e
	Riding (0.04 ^b) (McCrory & Turner, 2009a)
	Rollerblading (Fong, et al., 2007)
	Rowing ^e

	Scuba diving ^e	
	Surfing ^e	
	Swimming ^e	
	Tai chi ^d (Zetaruk, Viola'n, Zurakowski, & Micheli, 2005)	
	Yoga ^e	
	Walking ^e	
Moderate risk	Aerobics (Requa, et al., 1993)	
	Airsoft ^e	
	Alpine skiing (3.18 ^c) (Florenes & A., 2009)	
	Athletics/Track & Field (7.7% ^d) Field (shot, javelin, hammer) (158-286 ^b)	
	Cricket (1.2 ^a) (Ranson, Hurley, Rugless, Mansingh, & Cole, 2013; Stretch, 2003)	
	Dance (2.66 ^a) (Requa, et al., 1993)	
	Fencing (13% ^d) (Harmer, 2009a)	
	Gymnastics (0.62 ^a or 24% ^d) (A Junge et al., 2009; Kolt & Caine, 2009)	
	Ice-skating (mean 14% ^d) (Doherty et al., 2014)	
	Judo (mean 9.5%, 2.9 – 19.9% ^d) (Harmer, 2009b)	
	PE Classes ^e	
	Physical Theatre ^e	
	Playground Games ^e	
	Snowboarding (0.97 ^c or up to 28% ^d) (Fong, et al., 2007)	
	Squash (16% ^{d,e}) (Eime, Zazryn, & Finch, 2003; Fong, et al., 2007; Meyer, van Niekerk, Prinsloo, Steenkamp, & Louw, 2009)	
	Table tennis (7.9% ^d) (Shida, Shida, Suzuki, Murakami, & Yuza, 1992)	
	Touch rugby (1.1 ^a) (Fong, et al., 2007)	
	Track & Field (Alonso et al., 2010; Rauh & Macera, 2009)	
	High risk	5-A-Side Football (C 11.68 ^a) (Fong, et al., 2007)
		Ballet ^{a,d} (Allen, Nevill, Brooks, Koutedakis, & Wyon, 2012; Ekegren, Quested, & Brodrick, 2014)
Basketball (5.2 ^a , 3.85 ^c) (G. McKay & Cook, 2009; G. D. McKay, Goldie, Payne, & Oakes, 2001)		
Football (6.52/ C 34.83 ^a) (A. Junge, Cheung, Edwards, & Dvorak, 2004)		
Gaelic football (Fong, et al., 2007)		
Hockey (1000 ^b) (Murtaugh, 2009)		
Hurling (32.88 ^a) (Fong, et al., 2007)		
Karate ^d (Critchley, Mannion, & Meredith, 1999; Lystad, 2015; Zetaruk, et al., 2005)		
Martial arts (kicking) ^d (Gartland, Malik, & Lovell, 2001; Lystad, 2015; Zetaruk, et al., 2005)		
Riding (10.30 ^b) (McCrorry & Turner, 2009b)		
Rugby (C* 14 ^a) Rugby training (8.14 ^a) (Haseler, Carmont, & England, 2010; A. Junge, et al., 2004)		
Skateboarding/long boarding ^e		
Tennis (11.3 ^c or 6.9-25% ^d) (Pluim & Staal, 2009)		
Triathlon (4.70 ^a) (Vleck, 2009)		
Volleyball (C 5.5 ^a or 16-41% ^d) (Reeser, Verhagen, Briner, Askeland, & Bahr, 2006; Verhagen, 2009)		

^a risk/1000 exposure hours, ^b risk/1000 person years, ^c risk/1000 person exposures, ^d percentage of injury incidence to body, ^e expert opinion, C=competition

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A. McCarthy, A. Moore, L. Redhead, P. McLaughlin, A. Iorio, P. Chowdary (2015) *Development of Haemophilic Arthropathy of the Ankle: Results of a Delphi Consensus Survey on Potential Contributory Factors*. World Federation of Haemophilia Conference, Melbourne, Australia

McCarthy A, Moore A, Redhead L, McLaughlin P, Iorio A, Chowdary P (2015) *Using a Mixed Methods Research Approach to Drive Change in the Management of People With Haemophilia*. Physiotherapy UK Liverpool.

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**Protocol for
An Exploratory Study for Developing an Assessment Instrument for
Evaluation of Non-Haematological Factors and their Effect on the
Development of Joint Disease in Haemophilia.**

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Abbreviations used

BMI	Body Mass Index
LAS	Lateral Ankle Sprain
PWH	Persons With Haemophilia
KDHC	Katherine Dormandy Haemophilia Centre

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1 Abstract

Despite the great advances made in stabilising the condition of persons with haemophilia (PWH), devastating musculoskeletal consequences continue to occur suggesting the need for investigation not just into the haematological factors that predispose to joint disease but also non-haematological factors. Non-haematological factors will be identified using a Delphi procedure and an instrument will be designed to for assessment purposes. A purposive sample of expert patients, carers and clinicians will be invited to take part in the Delphi procedure. The instrument will be validated using a convenience sample of 15 PWH with clinically mild ankle joint arthropathy or no joint disease. This process will allow researchers to progress to the application of the instrument to pertinent patient cohorts with the intention of looking for any correlations between non-haematological factors and the tendency to develop haemarthropathy.

2 Background and Literature Review

Haemophilic arthropathy is a serious clinical consequence of the X - linked inherited bleeding disorders haemophilia A and B. These conditions are characterised by the either complete absence or decreased concentration of clotting factors VIII and IX respectively. Hypothetically, joint damage can be prevented by maintaining circulating factor VIII or IX greater than 5% at all times as joint damage is not seen in patients with this level of factor deficiency (categorised as mild), but this would not be feasible due to the high cost of factor replacement

therapy. Current treatment regimens therefore aim to keep factors $\geq 1\%$ (Rossbach 2010). It has been shown that prophylactic treatment begun ideally at initial diagnosis can prevent joint bleeding episodes in many subjects (Dunn 2005), however not all are equally protected. There is a variation in response to prophylactic treatment. Some people with severe haemophilia present with minimal bleeding episodes even on lesser factor intensive treatment regimens whereas others fully compliant on prophylactic treatment persist in bleeding into certain joints which are then described as target joints. Whilst there has been and continues to be a large volume of research concerning the medical haematological management and genetic origins of the condition, there has been little consideration of the non-haematological factors that may impact on clinical presentation.

A review of the literature that considers non-haematological aspects of clinical presentation indicates a general misapprehension regarding cause and effect; that they are established, as they undertake investigation into the therapeutic effect of various interventions without justifying their basis (Querol et al 2002; Seuser et al 1997). This literature review has not found a single study which has attempted to demonstrate causal relationships between non-haematological factors and bleeding patterns. However, with respect to the most common ankle injury, lateral ankle sprain (LAS), there is a wealth of research (e.g. (Beynnon et al 2002; Cordova et al 2002; Hiller et al 2011; McHugh et al 2007; Monaghan et al 2006)). Buzzard and Heim (Buzzard & Heim 1995) noted in their study of 19 children with

severe haemophilia (average age of 6.6years), that over a six month period 31 out of 37 reported ankle bleeds were associated with trauma and posited whether the other bleeds were due to ankle inversion injuries that were unrecognised at the time.

A review of this body of literature indicates that with respect to the ankle joint, factors that have been identified in relation to LAS may have an impact on bleeding propensity either directly or indirectly. Potential factors gleaned include joint hypermobility (Stewart & Burden 2004), reduced proprioceptive acuity (McKeon & Hertel 2008), ethnic origin (Grahame 2003), age (Waterman et al 2010), BMI (Tyler et al 2006) and ankle and foot biomechanics (Brown et al 2008; Willems et al 2005). Whilst these factors determined from literature review would seem good candidates for investigation there is a no consensus on the non-haematological factors or the magnitude of their influence in the development of haemophilic joint disease. In the absence of a consensus a generic assessment tool would not be appropriate for assessing the potential factors. Hence the need for this present study, which aims to develop an assessment tool for use with patients with haemophilia A and B.

2.1 Rationale for the study

Despite the great advances made in stabilising the condition of persons with haemophilia (PWH), devastating musculoskeletal consequences continue to occur (Dunn 2005) suggesting the need for investigation not just into the haematological

factors that predispose to joint disease but also non-haematological factors. These sequelae are occurring in developed countries with access to high cost treatment but more seriously in those where such care is not available. Many current physiotherapeutic and other interventions for these sequelae are based on experiential evidence which when subject to clinical reasoning does not always have an evidence informed foundation.

The overall aim of this programme of work is to assist health care professionals to be able to better target the management of PWH in order to prevent or ameliorate the destruction of joints due to haemophilic arthropathy. The research project has 3 phases (a detailed literature review and synthesis has already been carried out), and they are:

- A. A modified Delphi procedure using experts from haemophilia centres providing theme identification for inclusion in the assessment instrument.
- B. Piloting of an assessment instrument to ensure validity & reliability.
- C. Administration of the assessment instrument to the subject group generating quantitative data for analysis seeking to identify factors that may influence the development ankle bleeds in haemophilia.

The current protocol aims to cover phase A and B with a view to a further submission for Ethics approval once the tool has been validated to cover the activities stated in phase C. The aims, objectives and study design for each phase are described separately.

3 Study Overall Aim

To develop and validate an assessment instrument for use in musculoskeletal assessment of persons with haemophilia, through a combination of literature review and a consensus opinion on potential non-haematological factors that might contribute to joint damage garnered from experts in the field via a Delphi technique, using the ankle joint as a representative joint.

3.1 Overall Study Design

Phases A and B are stages within a greater programme of study. The overall programme is a sequential exploratory strategy mixed methods study. In this type of study an initial qualitative data collection and analysis is followed by a quantitative data collection and analysis whereby the results of the latter section build on the results from the former. It is cited as the strategy of choice when seeking to determine the distribution of a phenomenon within a given population and also when needing to develop an instrument because existing instruments are not adequate or available (Cresswell 2009).

4 Study Design: Establishing a consensus opinion of possible non – haematological factors contributing to the occurrence of ankle joint bleeds in persons with haemophilia using a modified Delphi technique approach.

4.1 General Design

This is a study to establish consensus from a purposive sample of expert patients, carers and clinicians using an electronically mediated Delphi procedure. Delphi technique is a structured communication method whereby a panel of experts responds to a questionnaire over a series of rounds with facilitator feedback between each round (Unknown 2011). A list of ranked factors which warrant further investigation will be generated.

4.1 Primary Objective

To establish a consensus of expert opinion on possible non - haematological factors affecting the development of ankle haemarthropathy in persons with severe or moderate haemophilia and to establish consensus on the urgency with which they need to be investigated.

4.1 Primary End Points

This study will be considered to be ended when statistical analysis indicates an acceptable level of concordance or agreement between the participants in the Delphi study. It is anticipated that this will occur after the third round (Rushton & Moore 2010).

5 Study Group

5.1 Inclusion Criteria

- Any person who considers themselves to be expert in the presentation of ankle arthropathy in haemophilia or breakthrough bleeding or non-

haematological aspects of haemophilia. For the purposes of this study, an expert is defined as a

- a. Any patient with isolated or dominant ankle arthropathy
 - b. A carer or guardian with an understanding of the factors that contribute to arthropathy
 - c. Clinicians across different specialties who either understand the factors that contribute to arthropathy or see patients with arthropathy
- Willingness to participate
 - Patients of any age may participate as long as the parent or guardian feels that they are competent to do so.
 - Access to the internet

5.2 Exclusion Criteria

- Clinicians unable to demonstrate their expertise
- Unable to complete the survey in English

5.3 Recruitment and screening

Experts will be sourced by direct approach to haemophilia treatment centre directors in the United Kingdom. Additionally, clinicians will be approached via special interest networks such as the Haemophilia Physiotherapy Group, the musculoskeletal working party of the UK Haemophilia Centre Doctor's Organisation and Haem.net (a web-based forum for allied health professionals).

5.4 Study procedure

A modified Delphi technique will be used with particular directives for each round (Rushton & Moore 2010). It will be conducted electronically. The first round of the Delphi will request up to 10 - 12 factors that may influence the occurrence of bleeding into the ankle. The second round will request that the generated items be ranked on importance to study. The third round will ask participants to continue the consensus building process having reviewed the outcome of round 2. At this point, if a level of consensus has been reached as determined by statistical analysis, the study would have achieved its primary endpoint (Rushton & Moore 2010). If however, a level of concord has not been achieved subsequent rounds will continue until investigators are satisfied that it has occurred.

The consensus items will be reviewed in the light of the investigator's original theory and clinical assessment tools identified from literature review, to inform the development of the assessment instrument. If items have been generated and ranked of high importance by the expert participants that are not part of the original theory, then further literature review will be undertaken to determine how best to assess for these and whether it is feasible to implement within the scope of this study.

5.5 Study procedures - Data collection

All experts will have details of their role (patient, carer/guardian, doctor, physiotherapist, nurse etc), and number of years of experience with to haemophilia recorded.

6 Statistical Analysis

50 experts will be recruited, aiming for 40 at the end of data collection, allowing for drop out. It is likely that the group will contain more clinicians than patients/carers as in normal care for this patient population the clinician: patient/carer ratio is weighted towards the clinicians (specialist nurse, physiotherapist and medical staff).

- A level of consensus will be set which will be used to retain or discard items; this is dependent on the number of items generated and so cannot be set in advance.
- A coefficient of variation will be established dependant on the number of response items generated (Rushton & Moore 2010). This will be used to establish whether consensus has been achieved by the third round.
- Kendall's coefficient of concordance will be applied in order to assess agreement between raters (Hicks 2009).

7 Data Handling and Record Keeping

Information about patients will be kept confidential and managed in accordance with Trust Data Protection Guidance, which incorporates the Data Protection Act of 1998. Data will be pseudoanonymised at the earliest opportunity and access to patient identifiable data will be restricted to the investigators and members of the direct health care team. Copies of consent forms, case record forms, and results will be filed in dedicated study folder and stored in a locked room dedicated for

clinical trials and studies. Access to this information will be restricted to the investigators only.

All patient identifiable data will be stored on NHS computers and NHS approved devices in accordance with Trust Data Protection guidance. Data will be collated using excel databases held on the said password protected computers. Complete confidentiality will be maintained at all times. Only the investigating team will have access to the data.

8 Ethical Issues

The proposed study is non-interventional study, with the minimum inconvenience.

9 Funding

This study has received funding from the Private Physiotherapy Education Fund.

10 Sponsor

Royal Free Hampstead NHS Trust is the sponsor of the study and the NHS Indemnity will apply for this study.

11 Publication Plan

The results of the study will be presented internally, and at National and International meetings and in peer-reviewed journals. These might include

Chartered Society of Physiotherapy Congress musculoskeletal programme, World Federation of Haemophilia Conference, and Haemophilia Journal.

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*Represents web pages where the author is not known.

eAppendix 2 Delphi Process Funding Letter



November 28, 2016

Dr Pratima Chowdary,
Katherine Dormandy Haemophilia Centre
Royal Free Hospital,
Pond St,
London,
NW3 2PF

Re: Pfizer Reference # WS2361082
External Reference #

Dear Dr Chowdary,

The Haemophilia IIR Grant Review Committee has reviewed your proposal, entitled Haemophilia Arthropathy -Development and validation of a clinical assessment tool for evaluating the prevalence and influence of non-haematological factors to facilitate the optimisation of regular prophylaxis to patient needs, and is pleased to inform you that Pfizer is interested in supporting your research with funding and/or drug.

The total amount of funding you requested is £85,489 GBP.

Please complete and return the accompanying Site Information Sheet to begin the contracting process. For those studies being conducted in the United States and Puerto Rico where funding is provided, a completed IRS Form W-9 is required.

Pfizer support is contingent upon the receipt of:

- Final research protocol*
- IIR Agreement executed between Pfizer and your institution
- IRB/IEC approval (as appropriate)
- Regulatory response (see enclosed guidelines)

*Please be aware that if the research described in your final protocol is materially different from that presented in your original proposal, then Pfizer reserves the right to reconsider its support.

If you have not obtained IRB approval and/or executed the IIR Agreement with Pfizer within six (6) months from the date of this letter, then funding for your grant cannot be guaranteed. Although this letter signifies Pfizer's intention to support your proposal, Pfizer is not committed until an agreement has been fully executed.

To ensure that the Pfizer safety and pharmacovigilance obligations are met, Serious Adverse Events (SAEs) must be reported to Pfizer for all clinical studies using a Pfizer product. In addition, for IIR studies using a Pfizer device or Pfizer product packaged with a device, reportable events include not only SAEs but Device Incidents and Device Near-Incidents. The reporting of these events to Pfizer does not relieve you or your institution of the responsibility to report any such event to the FDA or to the local regulatory authorities that govern your institution. Please review the accompanying IIR SAE training materials carefully to fully understand your Pfizer Safety reporting obligations.

Pfizer recognizes that carefully conducted clinical trials are the fastest and safest way to find treatments to improve health. As such, Pfizer encourages you and your institution to add this study to the FDA's www.clinicaltrials.gov database. Pfizer recognizes that the availability of clinical trial listings and results are critical to the communication of important new information for the medical profession, patients, and the public.

If you have questions, please contact me on 0776 8548723.

We look forward to working with you.

Yours sincerely,

Lisa Young

Medical Scientific Relations – Haemophilia – Pfizer UK

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e Appendix 3 Delphi Funding letter PPEF

Ann McCarthy MCSP
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Dear Ann,

Thank you very much for your application to PPEF for a grant under our Scheme for Research Projects.

The Trustees considered your application very carefully at their recent meeting and have decided to support your application.

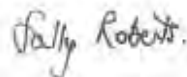
However they have decided to deduct the sum of £3,000 for your dissemination costs and Conference expenses. You may make a separate application for this at a later date.

Please would you be kind enough to complete, sign and return the enclosed documents and I will authorise payment of your award.

I would like to wish you every success with your project and the Trustees look forward to receiving your reports from you and a final report on completion of the project together with details of dissemination of the work.

With very best wishes

Yours sincerely,



Sally Roberts MCSP
Chairman of the Board of Trustees
The Private Physiotherapy Educational Foundation

E Appendix 4 Delphi Round 1 Survey

Thank you for agreeing to take part in this survey. This survey will help inform our on-going research into the influence of non-haemophilia factors that might contribute to joint damage in haemophilia. We are focussing on the ankle joint at this point.

The first question below will direct you to a full introduction.

*** 1. Are you a clinician?**

Yes

No

Dear Colleague

Thank you for agreeing to take part in this Delphi survey. For those of you who have not used this method before, it is a way of collating expert opinion where there is too little, too much or conflicting information. It can be adapted to suit specific situations. For further information I would refer you to the information contained via the link given below.

We are looking at the potential for non-haematological factors to influence the development of joint damage in severe/moderate haemophilia with specific reference to the ankle joint. Although regular factor replacement therapy (prophylaxis) is the standard of care, joint damage continues to be seen even in patients with excellent compliance. There is general agreement that joint damage is multifactorial and this is illustrated by the presence of minimal joint damage in about 10% of patients with severe haemophilia and the presence of severe joint damage in a few moderate haemophilia patients. This has been reviewed in depth by Raffini and Manno (link below). The aim of this study is to identify the non-haematological factors that might contribute to the development of joint damage, which will be used to develop and validate a clinical assessment tool.

In order to do this, I am asking you to list up to 10 factors that you think might have an impact. These factors may potentially increase the likelihood of bleeding or may independently contribute to joint damage. It may be helpful for us to provide you with some examples, therefore as a way of stimulating your ideas, the following may be helpful:

- specific biomechanical factors
- over or underflexibility
- their activity choices
- specific kinds of injuries or accidents
- balance problems

It would be helpful if you can give me the rationale for your suggestion but it is not absolutely necessary.

I will then collate the responses from everyone taking part, where items are similar I may choose to put them under an umbrella term. This list will then be put into the second questionnaire on Survey Monkey and I will ask you to rank them in order of importance. There may be a third round if consensus has not been achieved with round 2.

Taking part in this survey should only take about 20 minutes of your time on approximately two - three occasions about 4 – 6 weeks apart.

Thank you once again for taking part!

Ann McCarthy

Delphi Method: http://en.wikipedia.org/wiki/Delphi_method

Raffini and Manno: <http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2141.2007.06490.x/pdf>

These questions provide us with information about your clinical background.

***2. What is your professional background? (Tick all that apply)**

- Consultant (haematologist)
- Consultant (trauma & orthopaedics)
- Consultant (orthopaedics, foot & ankle)
- Consultant (rheumatology)
- Consultant (rheumatology, foot & ankle)
- Consultant (rheumatology, connective tissue disease)
- Consultant (other)
- Nurse specialist
- Physiotherapist (haemophilia)
- Physiotherapist (musculoskeletal)
- Podiatrist
- Occupational Therapist
- Researcher/lecturer (please specify area in "other" below).
- Other

Other (please specify)

***3. For how many years have you specialised in your area of interest?**

- 1 – 5
- 6 – 10
- 11 – 15
- 16 – 20
- 21 – 25
- More than 25

Dear Study Participant,

Thank you for agreeing to take part in this Delphi study. For those of you who have not used this method before, it is a way of collating expert opinion where there is too little, too much or conflicting information. It can be adapted to suit specific situations. Please see the link below for further information. This study will help form our on-going research into the non-haemophilia things that might influence how haemophilia affects the ankle joint. The information that you provide will be used to design an assessment tool that will be part survey and part clinical testing. The assessment tool will then be tested on a small group of volunteers before being applied to a larger group. We are looking to establish whether there are any relationships between the items tested and development of ankle problems.

In order to do this, I am asking you to list up to 10 things that you think might impact on developing ankle problems. It is difficult to explain this properly without putting my ideas into your heads, but this may help you:

- physical things to do with the person, e.g. strength/weakness, flexibility/stiffness,
- to do with the way they live their lives, e.g. always careful/risk taker, choice of shoes
- their activity choices,
- specific kinds of injuries or accidents, e.g. tripping/stumbling/turning the ankle
- things that only occur in childhood or things that can happen at any time

It would be helpful if can give me a reason for your suggestion but it is not absolutely necessary.

I will then collate the responses from everyone taking part, where items are similar I may choose to put them under an umbrella term. This list will then be put into the second questionnaire on Survey Monkey and I will ask you to put them in order of how important they are to study or another way of putting this , how likely they are to have an impact. I may have to do this part more than once until the majority of participants agree with the majority of the order.

Taking part in this survey should only take about 20 minutes of your time on approximately three occasions about 4 – 6 weeks apart.

Thank you once again for taking part!

Ann McCarthy

Delphi Method: http://en.wikipedia.org/wiki/Delphi_method

These questions provide information about you as an expert patient.

***4. What is your age?**

- < 20
- 21 – 30
- 31 – 40
- 41 – 50
- 51 – 60
- 61 – 70
- 71 – 80
- 80 +

***5. How do you receive your factor replacement therapy?**

- Regular prophylactic doses
- Only when I need it, on – demand
- I do not need factor replacement

***6. At what age did you start regular prophylaxis?**

- <5
- 5 – 10
- 11 – 15
- 16 – 20
- 20 +

***7. How does haemophilia affect your ankle joints?**

- Right only
- Left only
- Both

***8. Approximately how many bleeds have you have into your ankle joints since your diagnosis?**

- 1 – 5
- 6 – 10
- 11 – 15
- 16 – 20
- 21 – 25
- More than 25
- Don't know

First round questionnaire: Establishing non-haemophilia factors that may contribute to bleeding.

This is the first round of the questionnaire for you to complete.

Please list up to 10 factors that you believe may contribute to the development of ankle problems in patients with Haemophilia.

9. Factor 1

Factor 1

Reasoning

10. Factor 2

Factor 2

Reasoning

11. Factor 3

Factor 3

Reasoning

12. Factor 4

Factor 4

Reasoning

13. Factor 5

Factor 5

Reasoning

14. Factor 6

Factor 6

Reasoning

15. Factor 7

Factor 7

Reasoning

16. Factor 8

Factor 8

Reasoning

17. Factor 9

Factor 9

Reasoning

18. Factor 10

Factor 10

Reasoning

20. Please explain the reasons you said it was “[Q19]” for you to provide the list of potential factors in response to the the previous question.

21. Any other comments?

Thank you again for taking part in this survey!

***19. How easy was it for you to provide the list of potential factors?**

- Easy
- Moderately easy
- Difficult
- Very difficult

E Appendix 5 Delphi Round 3 Survey

Establishing the non-haematological factors that may affect bleeding -

Dear Colleagues,

Welcome to the third and final round of the Delphi study. The response rate for round 2 was an excellent 77%. So thank you very much for your continued support and we're nearly there. Firstly, we are presenting you with the results so far in graphical form so that you can see how the group has voted. Following this is a very short survey consisting of only the factors that didn't reach consensus in round 2, one factor that has been clarified further to feedback and 2 new factors totalling 14 in all. So this should be a very quick round to perform!

It is our hope to be able to devise strategies to investigate as many of these factors as possible within the programme. However, with certain factors the "answer" is already available within the literature such as inhibitor formation and severe bleeding phenotype and so we will not be investigating those per se but will look to see if they relate to other factors.

The results will also be published in full including how the consensus levels etcetera were decided upon. We'd like to thank you once again for your support; it truly is invaluable. We hope that together we can help achieve even better outcomes for those at risk of developing arthropathy.

Kind regards,

Ann McCarthy

Physiotherapy PhD Student, Katherine Dormandy Haemophilia Centre, Royal Free London NHS Foundation Trust

Supervisors

Professor Ann Moore, Centre for Clinical Research, University of Brighton

Dr Pratima Chowdary, Katherine Dormandy Haemophilia Centre, Royal Free London NHS Foundation Trust

Dr Lucy Redhead, School for Health Professions, University of Brighton

Establishing the non-haematological factors that may affect bleeding -

This is Round 2 Feedback

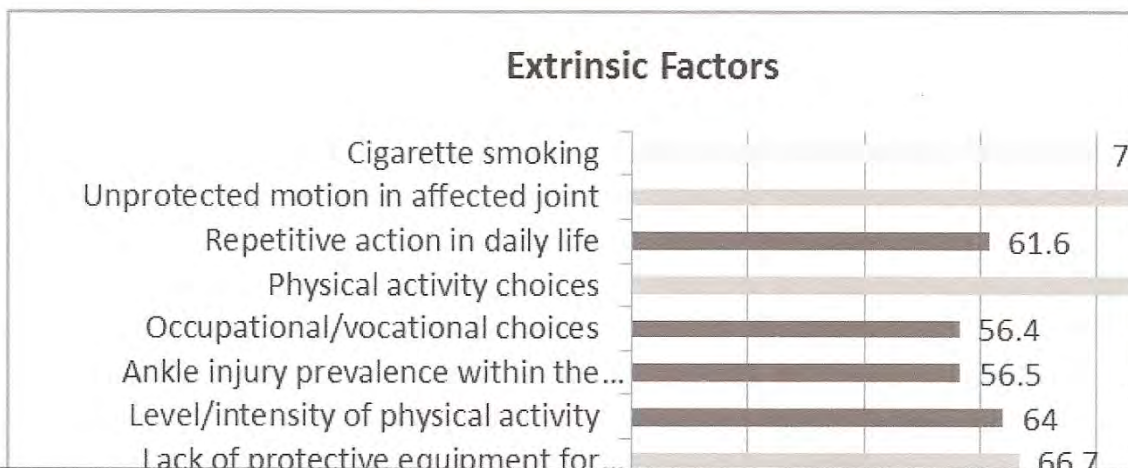
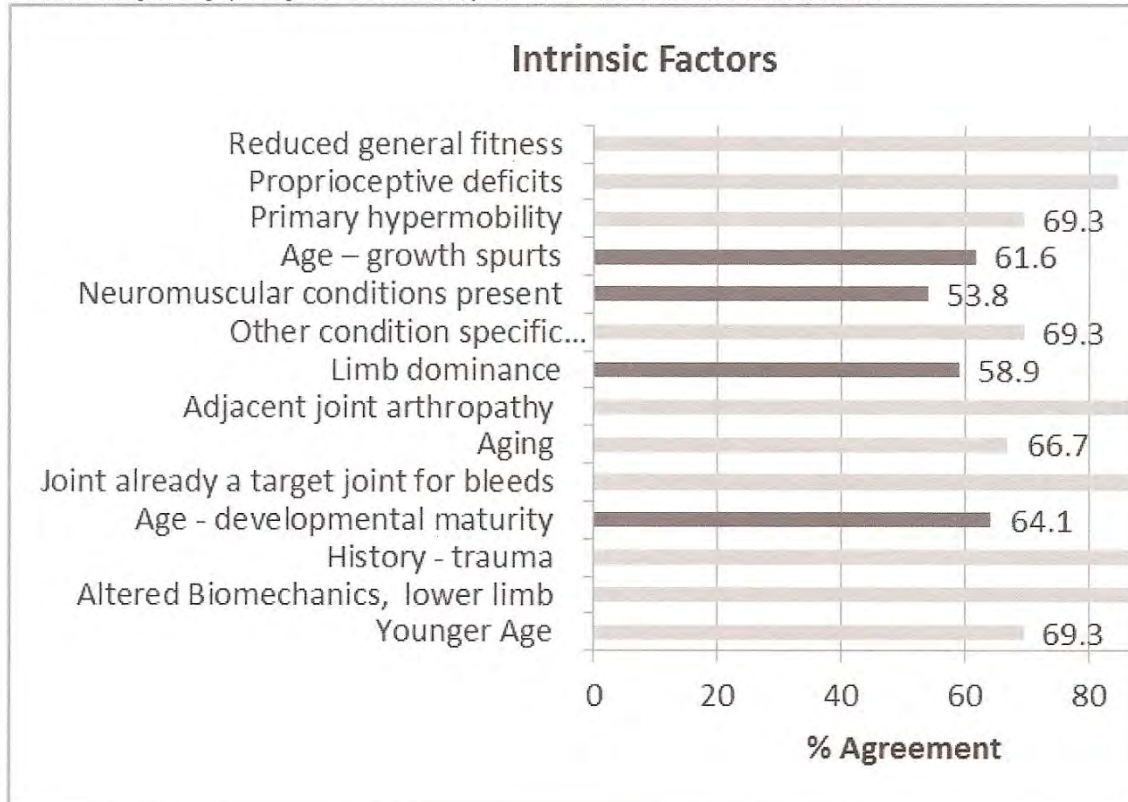
(Please note that in Internet Explorer, if the warning pops up regarding secure content, please click on "no" or the graphs will not show)

The level of agreement or consensus set by the research team was 60% and the level of importance for including factors in potential future studies was 4 or greater on the Likert scale.

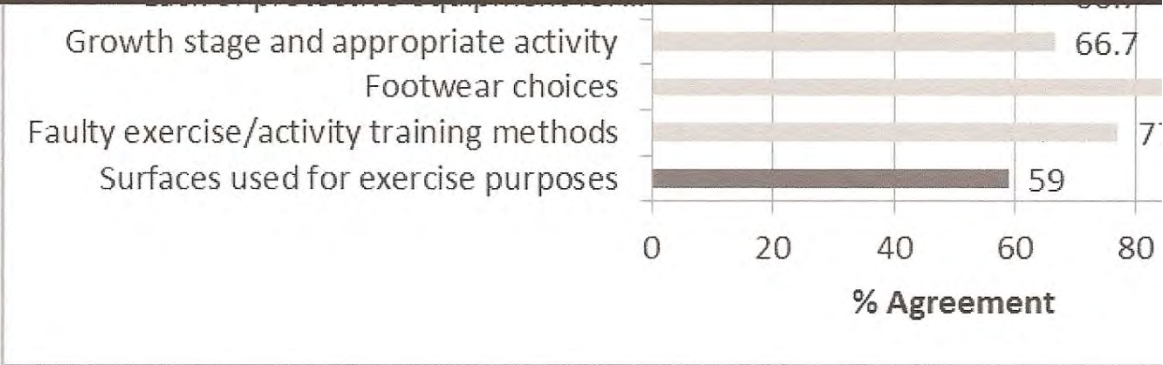
Where $\geq 60\%$ of the panellists scored an item from 4 - 6 on the Likert scale, it is likely to be included and if $\geq 60\%$ of the panellists scored an item from 1 - 3 on the Likert scale it is likely to be discarded.

Items not achieving a clear consensus either way and are borderline have been put forward for further consideration.

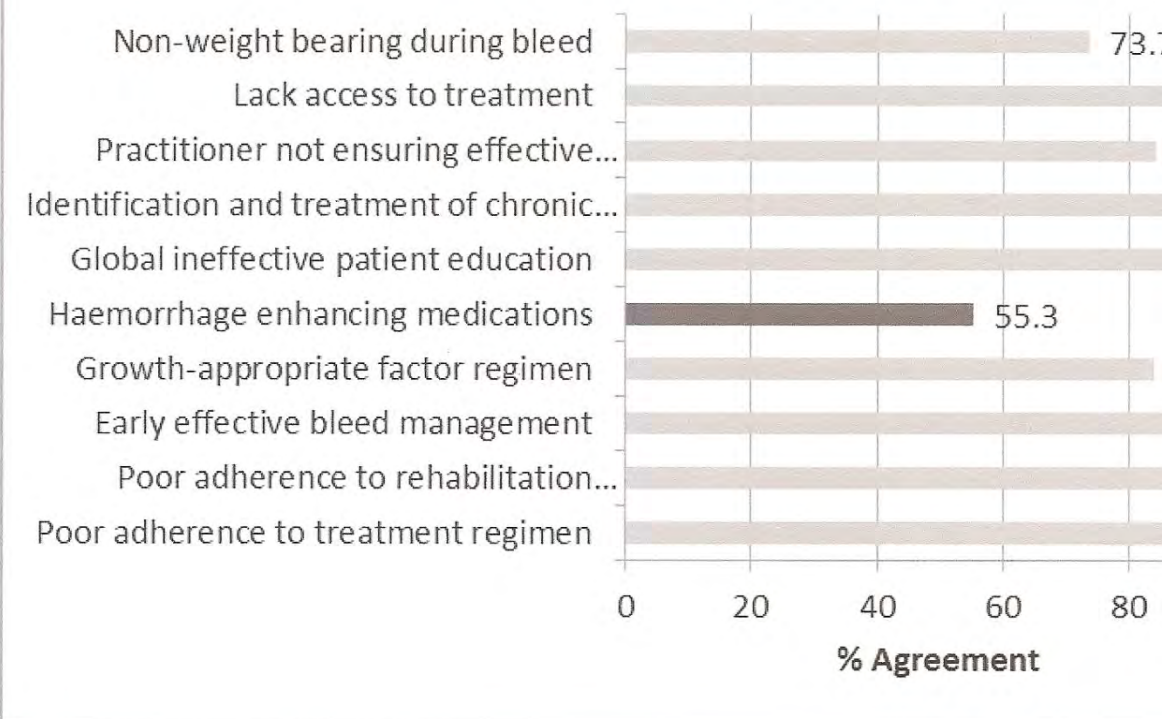
The colour coding for the graphs is: green = taken forwards, yellow = discarded and red = re-submitted to round 3



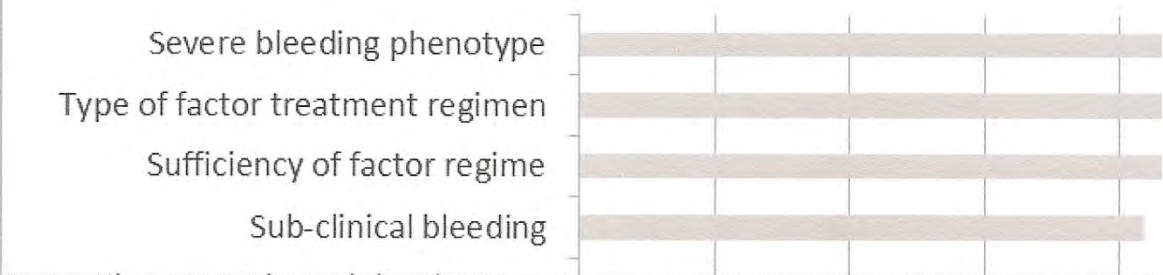
Establishing the non-haematological factors that may affect bleeding -



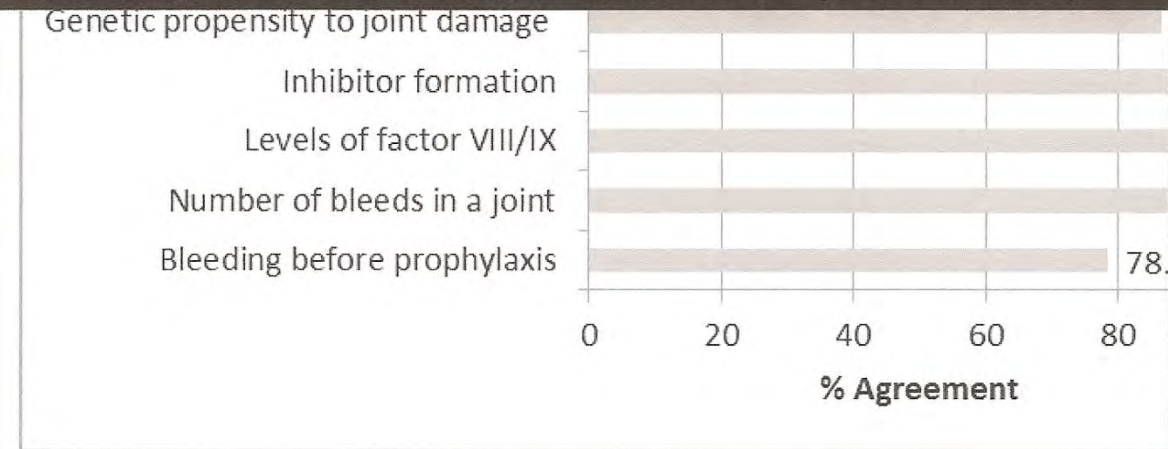
Compliance, Education Factors



Haematology Factors



Establishing the non-haematological factors that may affect bleeding -



*1. Sorry to be asking this again, but what is your professional background?

- Consultant (medical)
- Consultant (physiotherapist)
- Consultant (nurse)
- Consultant (podiatrist)
- Consultant (other)
- Clinical Specialist (Physiotherapist)
- Clinical Specialist (Nurse)
- Clinical Specialist (Other)
- Physiotherapist/Physical Therapist
- Nurse
- Podiatrist
- Researcher (please specify below)
- Academic (please specify below)
- Paediatrics
- Adult
- Other

Other (please specify)

Establishing the non-haematological factors that may affect bleeding -

*2. What are your specialist areas?

- Haemophilia, Haemostasis and Thrombosis
- Trauma and Orthopaedics
- Rheumatology
- Musculoskeletal
- Foot and Ankle
- Connective Tissue Diseases
- Other

Other (please specify)

Round 3 Instructions

3 to 12 below are the borderline factors brought forward from round 2 and are presented with the group results. Please consider your original position in light of this and decide whether the item should be kept (in) or discarded (out). The please tell us briefly your reason for this.

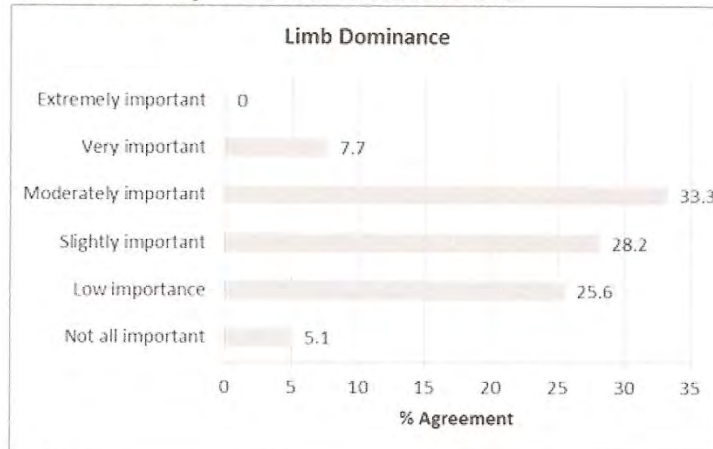
Should there be a lack of consensus again on any item, these comments will help us decide the outcome for the item.

For factors 13 - 16 (on the next page), these are either new or clarification of previous factors. Please rank them as you have done previously using the Likert scale provided.

Establishing the non-haematological factors that may affect bleeding -

*3. Limb dominance

More bleeds may occur in the dominant limb.



In

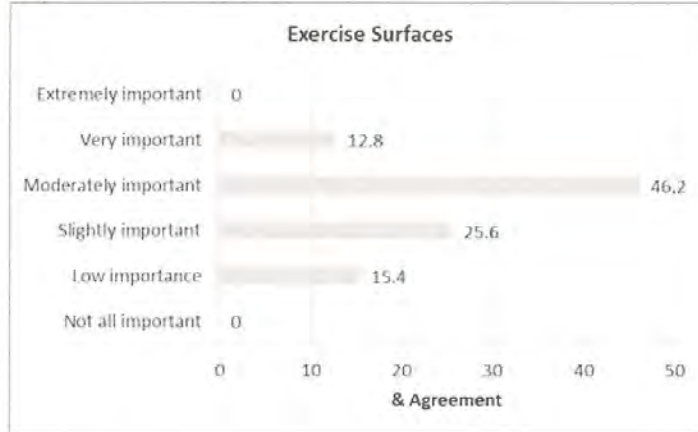
Out

Why?

Establishing the non-haematological factors that may affect bleeding -

***5. Surfaces used for exercise purposes**

There is some evidence that exercise surface can affect risk of injury. Uneven surfaces could result in loss of balance. Harder ground could lead to increase stresses on the joint.



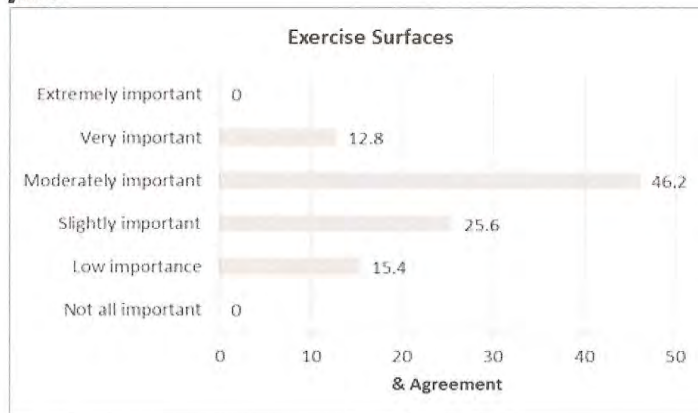
- In
- Out

Why?

Establishing the non-haematological factors that may affect bleeding -

***5. Surfaces used for exercise purposes**

There is some evidence that exercise surface can affect risk of injury. Uneven surfaces could result in loss of balance. Harder ground could lead to increase stresses on the joint.



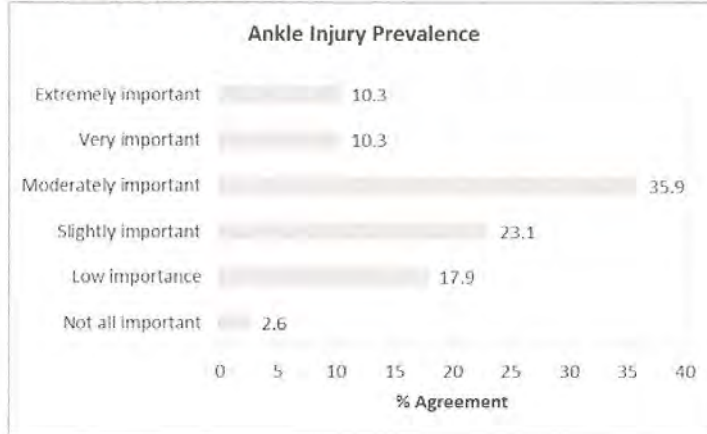
- In
- Out

Why?

Establishing the non-haematological factors that may affect bleeding -

***6. Ankle injury prevalence**

It is proposed that the activity levels within the haemophilia population have normalised and the prevalence of ankle disease reflects the fact that the ankle is one of the most commonly injured joints.



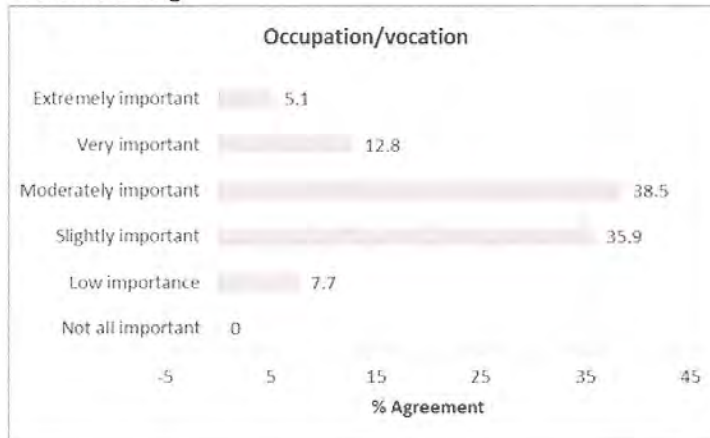
- In
- Out

Why?

Establishing the non-haematological factors that may affect bleeding -

***7. Occupation/vocation**

Jobs requiring heaving lifting or prolonged standing may increase ankle loading and so risk of bleeding.



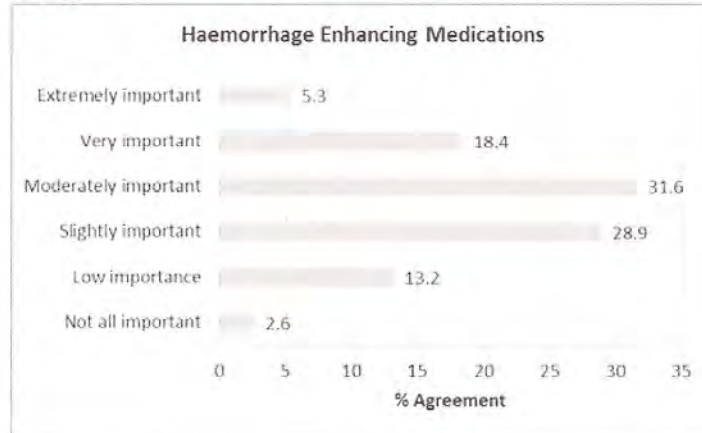
- In
- Out

Why?

Establishing the non-haematological factors that may affect bleeding -

*8. Haemorrhage enhancing medications

The potential of medications for other conditions to directly affect the propensity to bleed.

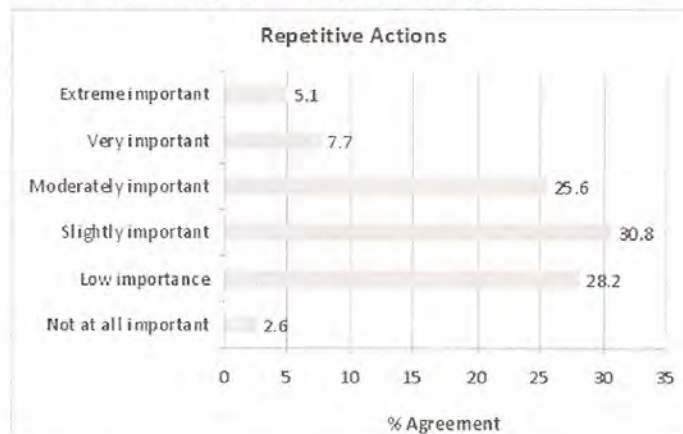


In

Establishing the non-haematological factors that may affect bleeding -

*9. Repetitive action in daily life

It is suggested that normal low load repetition such as when driving may be enough to overload the ankle joint leading to bleeding.



In

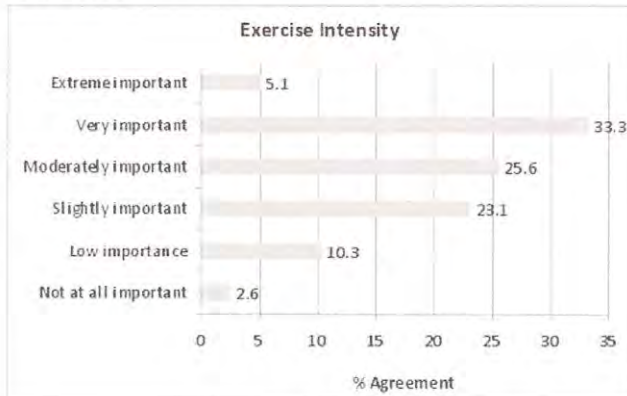
Out

Why?

Establishing the non-haematological factors that may affect bleeding -

*** 10. Level/intensity of physical activity**

High level activity or highly intensive activity might lead to subclinical bleeding within the weightbearing joints. Also, plainly suggested that those who exercise more sustain more bleeds.



In

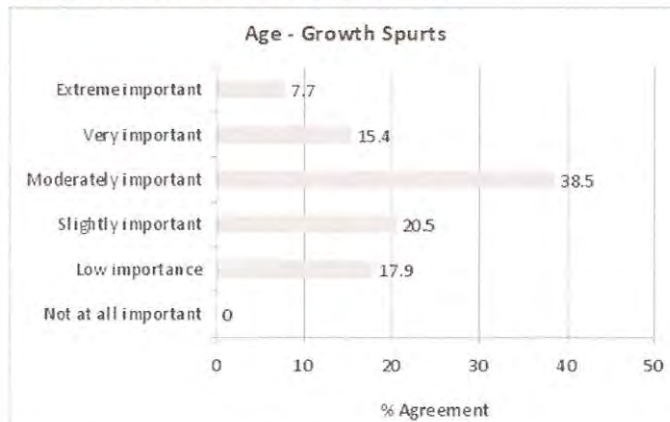
Out

Why?

Establishing the non-haematological factors that may affect bleeding -

*** 11. Age – growth spurts**

During a growth spurt, the child's rate of bone growth out-strips the lengthening of muscles and tendons, resulting in what should be temporary alterations such as shortened muscles and weaker ligaments. This may result in periods of time where the child is biomechanically more vulnerable.



In

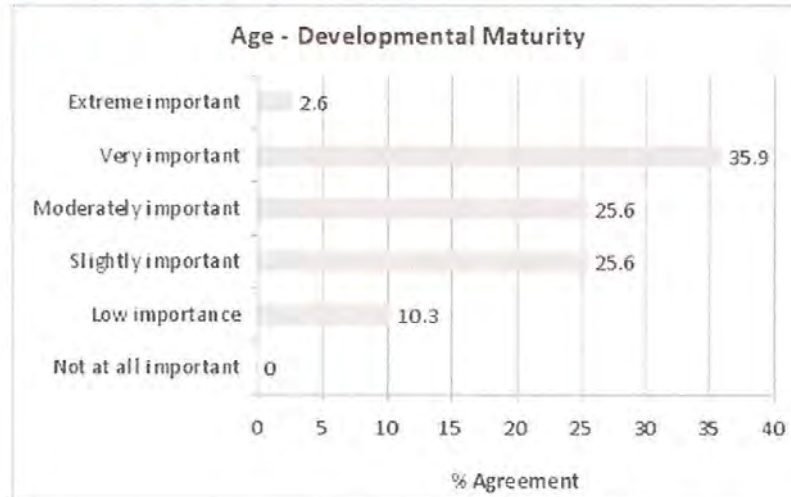
Out

Why?

Establishing the non-haematological factors that may affect bleeding -

* 12. Age - developmental maturity

At certain points the child is unable, due to neuro-developmental status, to perform functionally as well as an adult leading to an increased risk of injury. For instance they will have poorer balance, ligamentous laxity, less developed motor strategies and increased motion at joints.



In

Out

Why?

13. Specific foot & ankle biomechanics and anatomy

The ankle joint is subject to high stresses and demands. It is suggested that its shape and configuration contribute to this. Also there are many alterations in the ankle/foot posture and motion that could increase risk of bleeding or injury such as rearfoot valgus, over-pronation of the foot in the stance phase of gait or high-arched foot posture.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Specific foot & ankle biomechanics and anatomy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Establishing the non-haematological factors that may affect bleeding -

14. Weight/BMI

Increased BMI has been linked to the occurrence of ankle sprain and other injuries. It is also linked to increased forces applied to the ankle joint. Also suggested is a higher rate of subclinical bleeds.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Weight/BMI	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

15. Activity levels at younger age

Children are busy. Children prior to formal sit-down teaching spend more of their day at play.

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Activity levels at younger age	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

16. Communication at younger age

Children .. may be having small bleeds before they can express themselves

	Not at all important	Low importance	Slightly important	Moderately important	Very important	Extremely important
Communication at younger age	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

17. That was the final factor. Do wish to make any final comments or give feedback to the research team?

Thank you for completing the final survey!

Please look out for the published results to see full details of the survey.

E Appendices 6, 7 & 8 are large spreadsheets containing example raw Delphi Process study data which can be accessed on application to the University of Brighton.

**Protocol for
Gluteal Muscle Activation During the Star
Excursion Balance Test.**

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1 Abstract

The star excursion balance test was designed to test a person's dynamic balance however the original procedure is time consuming. Previous studies have recommended reductions in number of warm up repetitions and in directions of reach. A study has also examined the lower limb muscle activation. For the purposes of the main doctoral study, it is required to ensure that the reach directions chosen are most efficacious in providing useful data. This would include the functional ability of the participant around the pelvis and in particular the recruitment of gluteus medius and maximus muscles. Current studies do not indicate muscle activity in this region. Therefore the purpose of this study is to assess for the activation of these muscles during the aforementioned test and analyse which directions produce the greatest challenge to them.

2 Background and Literature Review

The SEBT has been described as a functional test that quantifies lower extremity reach while challenging an individual's limits of stability (Olmsted, Carcia, Hertel, & Shultz, 2002). It looks for sensorimotor deficits whilst challenging strength and motor co-ordination also. As the test challenges hip, knee and ankle motion and control the test could also be said to partly examine lower limb biomechanical efficacy. The tool has been shown to be reliable and be able to detect impairments

between healthy and injured individuals, and also within subject for injured to non-injured side differences. However, the full testing procedure as described is lengthy and time consuming with the recommendation of 6 practice reaches in each of the 8 directions and 3 recorded trials on both legs.

Due to the lengthiness of the procedure studies have been undertaken looking at streamlining by utilising any redundancy in the testing directions (Hertel, Braham, Hale, & Olmsted-Kramer, 2006) and number of practices required to reach stability (Robinson & P.A. Gribble, 2008). Although this resulted in a streamlined version using 3 reach directions, with 4 practices and 3 recorded trials, there has been challenge to this whereby it is claimed that the error margins on the original trial directions research are such that the results cannot be supported (Munro & Herrington, 2010) but this is when the test is being used to monitor change. Moreover, other authors have used a reduced reach direction protocol apparently achieving acceptable results, and using different directions to those recommended originally (no explanation proffered) (Plisky, Rauh, Kaminski, & Underwood, 2006). Streamlined directions as per Hertel et al. (2006) are anteromedial (AM), medial (M) and posteromedial (PM) which produced the greatest challenges to balance. Plisky et al. (2006) and Hubbard et al. (2007) utilised Anterior (A), PM and posterolateral PL.

Reduced protocol has been shown to delineate differences within patients with unilateral chronic ankle instability (CAI) and normal subjects and also in a prospective study it has been shown to indicate risk of lower limb injury. The former used AM, Med and PM vectors. The latter study used AM, PM and PL vectors.

With respect to main study a protocol of 4 directions is suggested: Ant, AM, PM & PL to combine both reduced protocols and also include the anterior direction previously shown to require greatest quads activity (Earl & Hertel, 2001). Reliability is high. MCID 6- 8% normalised reach. Pliskey et al. (2006) found a 4cm difference in measures was indicative of risk of lower limb injury in a cohort of high school basketball players.

2.1 Rationale for the study

Previous studies have recommended streamlining the SEBT in order to reduce the testing time with regards to the number of directions and number of trials needed. However, subsequent studies have not utilized these recommendations but have favoured alternative but reduced numbers of test directions without explanation. This makes direction selection unclear. This study represents a preliminary work for a larger body programme which in part requires the functional efficacy of the gluteal muscles (medius and maximus) to be examined. Earl and Hertel (2001) did examine the muscle activity in the leg during the various reach directions but did not include any pelvic muscles. Therefore, the purpose of this study is to examine gluteus medius and gluteus maximus activity in each of the reach directions in order to facilitate the selection a reduced direction protocol.

3 Study Overall Aim

To enable selection of the ideal SEBT protocol that maximally challenges the lower quarter without unnecessary redundancy. A secondary aim is to establish SEBT procedures for the main study.

4 Study Design

This is a repeated measures experimental design. 10 healthy participants will be recruited and will perform the SEBT whilst gluteus medius and maximus muscle activity is recorded via EMG.

5 Study Group

5.1 Inclusion Criteria

- Over 18 years of age.
- Able to understand the Participant Information and Consent forms in English.

5.2 Exclusion Criteria

- Any lower limb injury in the last 6 months.
- Any ear or eye condition or injury that could affect balance.
- Any history of head injury.
- Any infectious skin condition of the foot.

5.3 Recruitment and screening

Volunteers will be recruited by poster and announcement at the host institution.

5.4 Study procedure

Volunteers will attend the Human Movement Laboratory, University of Brighton, the purpose of the study and test procedures will be fully explained and informed consent taken. Skin will be prepared for EMG and electrodes placed. Before testing, participants will be asked to warm up for 5 minutes. Following this maximum voluntary isometric contraction (MVIC) will be collected for both muscles. The left leg will be tested first in each subject replicating the procedure of Earl and Hertel (2001). For gluteus medius (GMed) the side plank with test leg down has been shown to produce a maximal contraction and for gluteus maximus (GMax), the plank with hip extension has been shown to do the same and may be used to gain MVIC.

The participants foot will be measured to allow for centralization over the test's centre. The SEBT will then be demonstrated. The test order will be A, AM, M, PM, posterior (P), PL, lateral (L) and anterolateral (AL) (Earl & Hertel, 2001). 6 practice circuits will be followed by an adequate rest and then 5 recorded reaches will be performed in each direction. For exact participant instructions see the table below.

Name	Star Excursion Balance Test (SEBT)
Purpose	Assesses intra and inter subject variability in lower limb dynamic balance, strength and co-ordination.
Equipment	Space (approx. 1.9m ²) to place a grid on the floor using tape or similar. Non-permanent marker. Tape measure/s.
Procedure	Measure participant's leg length in supine (ASIS to medial malleolus tip). Explain procedure and demonstrate. Use coin toss to determine which leg will be tested first. The test will occur barefoot. Practice trials will be performed immediately prior to testing. Practice trials will occur in a clockwise/anticlockwise fashion to limit fatigue effects. 3 measured trials will be performed in each reach vector. The maximum

	<p>reach with the most distal point of the foot will be marked and then measured at the end of the testing procedure. Greatest length will be used for analysis. The reach distance will be normalised for leg length as per calculation below.</p> <p>The participant's foot length will be measured and placed with the foot exactly on the centre of the grid. Marks will be placed to allow easy return to the same spot. With hands on hips, the participant will reach as far as possible along the given vector and lightly touch the ground without taking any weight on the reach leg. This will be marked by the researcher. The participant must then return to the start position without touching down where they may then assume a double stance. There will be 15secs rest between trials and 1mins rest between reach directions.</p> <p>A trial will be considered failed and repeated if:</p> <ol style="list-style-type: none"> 1. Person did not touch down at full reach 2. Lost balance at any point 3. Lifted the stance foot 4. Did not maintain stance position at beginning and end for 1 sec.
Statistics	<p>Normalised maximum excursion distance = distance/leg length X 100. Between limb differences. Order (size) of differences.</p>

5.5 Study procedures – Data acquisition

EMG data will be collected from the muscles during MVICs to allow for a percentage comparison. Raw EMG data will be low-pass filtered at 500Hz and high-pass at 10Hz. It will be integrated to remove the baseline. Root mean square (RMS) will be calculated over a 10-sample period. The average RMS value will be calculated from a 1 second window at the peak of the MVIC and from 100 ms window around the peak of the SEBT trials. The window is smaller in SEBT due to the speed variation during the trials. The average RMS value for each muscle for each trial was normalized with respect to its MVIC value and used as the dependent variable.

6 Statistical Analysis

ANOVA. Normalized EMG values in each direction. Separate test for each muscle. “ Six 1-within-factor ANOVA”. In the event of a significant ANOVA, a Tukey’s post hoc test will be run to identify significant differences in normalized EMG activity between specific directions of the test.

7 Data Handling and Record Keeping

Information about participants will be kept confidential and managed in accordance with University Data Protection Guidance, which incorporates the Data Protection Act of 1998. Data will be pseudoanonymised at the earliest opportunity and access to participant identifiable data will be restricted to the investigators.

8 Ethical Issues

The proposed study is non-interventional study, with the minimum inconvenience.

8.1 Safety

The proposed clinical assessment is considered to exert minimal physical strain on the individual and an inclusion criterion requires that the individual is healthy.

9 Publication Plan

Unknown at this time.

10 References

- Earl, J. E., & Hertel, J. (2001). Lower-extremity muscle activation during the Star Excursion Balance Test. *Journal of Sport Rehabilitation*, 10(2), 93 - 104.
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E Appendix 10 SEMG Study of Star Excursion Balance Test Information

Sheet

University of Brighton
Clinical Research Centre for Health Professions

Participant Information Sheet

1 Study title

Gluteal Muscle Activation During the Star Excursion Balance Test.

2 Invitation

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

3 What is the purpose of the study?

This study is trying to find out how certain of your gluteal (buttock) muscles work during a standard balance test called the Star Excursion Balance Test and whether certain directions work those muscles harder than others.

4 Why have I been invited?

You have been invited to take part in this study because you are basically fit and healthy with no history of injury to the leg or your head, and no history of ear or eye problem that might affect your balance.

5 Do I have to take part?

It is up to you to decide; it is totally voluntary. We will describe the study and go through this information sheet, which we will then give to you. Please take it away and decide whether you would like to help us in this research. If you decide to take part, then please read and sign the attached Consent Forms and return one to us in the envelope provided, keeping a copy for your own records. You are free to withdraw at any time, without giving a reason. You will not be affected in any way by a decision not to take part or withdraw.

6 What will happen to me if I take part?

You will be asked to come to the Human Movement Laboratory where we will use electromyography to assess how hard your muscles work during the test. This procedure does not cause any discomfort although the buttock area will have to be partly exposed to attach the electrodes, but you can return your clothing straight away. You will then be asked to perform a maximum contraction of the muscles to get a comparison reading and then perform the balance test. This should not take more than 30minutes in total.

7 What will I have to do?

As stated above, you will be asked to attend the Human Movement Laboratory. We would also ask that you do not partake of alcohol for 24 hours prior to the study as this may have a residual effect on your ability to balance. Please bring shorts and trainers with you, although the balance test will be performed barefoot.

8 What are the possible disadvantages and risks of taking part?

The risks of taking part are very low. This is a standard test often used with young populations. There will be no disadvantages to you in taking part. Please inform me

immediately during the testing if you should feel any discomfort or are concerned in any way.

9 What are the possible benefits of taking part?

There may not be an immediate benefit to you in taking part in this research as it is a preliminary study intended to inform further studies on a population group with haemophilia. But the information will allow us to proceed and we hope to improve our understanding of the things that contribute to the development of ankle arthritis in people with haemophilia.

10 What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might have suffered can be addressed by contacting my supervisor, Dr Lucy Redhead. For contact details see the bottom of the information sheet

11 Will my taking part in the study be kept confidential?

Yes. The information or study data will be kept until the series of studies is completed when it will be destroyed in approximately 2 years.

12 What will happen to the results of the research study?

If the test study is successful, we will then go on to apply them in a new assessment tool with a cohort of people with haemophilia.

13 Who has reviewed the study?

This study has been reviewed and approved by the Faculty of Health and Social Science Research Ethics and Governance Committee, University of Brighton.

14 Contacts for further information

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University of Brighton
Clinical Research Centre for Health Professions

Participant Consent Form

Title of Project: Gluteal Muscle Activation During the Star Excursion Balance Test.

Name: _____

Initials

Date of birth: _____

Name of Researcher: Ann McCarthy

- 1. I confirm that I have read and understand the information sheet which included a statement concerning the purpose, methods, demands, possible risks and inconveniences of this study dated for the above study. I have had the opportunity to consider the information and ask questions, which have been answered to my satisfaction.
- 2. I will inform the principal investigator if I have any symptoms of pain or discomfort during or after the clinical tests.
- 3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.
- 4. I have the right to ask to see the data collected about me and if anything is incorrect, I can ask for it to be corrected.
- 5. I agree to take part in the above study.

.....
Name of Participant, Date, Signature

.....
Name of Researcher, Date, Signature

Upon signing, the participant will retain a copy of this form, and the another will be held in the participant's research record.

**Proposal and Protocol for:
Evaluation of the Effect of Musculoskeletal and
Exercise Factors on the Development of Joint
Disease in Haemophilia**

Investigators and Key Study Personnel

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Abbreviations used

BMI	Body Mass Index
LAS	Lateral Ankle Sprain
PWH	Persons With Haemophilia
MRI	Magnetic Resonance Imaging
HJHS	Haemophilia Joint Health Score
RA	Rheumatoid Arthritis
OA	Osteoarthritis
NHS	National Health Service
FDQ	Functional Dyspraxia Questionnaire
US	Ultrasound
HEAD-US	Haemophilia Early Arthropathy Detection with Ultrasound Score

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1. Abstract

Joint arthropathy secondary to recurrent bleeds is the most disabling complication in persons with haemophilia (PWH) and despite the advances made in the haematological management including regular prophylaxis, the haemophilia community's goal of no or minimal joint damage is yet to be realised. This suggests a need for further research into the pathogenesis of haemophilic arthropathy. Development of haemophilic arthropathy is believed to be multifactorial, although the role of non-haematological factors has been poorly studied. To address this gap, potential non-haematological factors were identified by experts through a Delphi survey. These factors can be broadly categorised as musculoskeletal factors intrinsic to the patient, factors related to compliance, education and non-haematological management, extrinsic factors affecting musculoskeletal system and underlying haematological factors. The current study proposes to look into the intrinsic musculoskeletal and exercise-related factors that could potentially influence the development of haemophilic arthropathy. Based on expert opinion and literature review an assessment framework has been developed for evaluating these factors. The assessment includes validated clinical tests and surveys from literature, modified and adapted for PWH. This multi-centre study will assess a cohort of people with and without haemophilia, and with and without ankle joint disease. The data will be analysed to identify factors that either initiate the development of haemophilic arthropathy and/or perpetuate its progression. This will lead to greater personalisation of care through characterisation of an arthropathy phenotype independent of their haematological phenotype. The primary outcome is identification of patients who might benefit from a more intensive regimen for non-modifiable risk factors and targeted rehabilitation strategies for modifiable factors. Secondary outcomes include developing an evidence base for advice on appropriate physical activity and sports.

2. Background

2.1 Literature Review

Haemophilic arthropathy is a serious clinical consequence of the X - linked inherited bleeding disorders haemophilia A and B. These conditions are characterised by the either complete absence or decreased concentration of clotting factors VIII and IX respectively. Current standard of care in countries where the healthcare system permits, includes regular self-infusion of the missing factor two to three times a week to prevent joint damage. The underlying principle is to maintain a base level of 1% or greater of circulating factor as current evidence shows the number of breakthrough bleeds is related to the total time spend at low levels (Collins 2012). It has been shown that prophylactic treatment begun ideally before the age of three can prevent joint bleeding episodes in many subjects (Valentino et al 2012), however the outcomes are not consistent, suggesting some inter-individual variability. 10 – 15% of people with severe haemophilia present with moderate

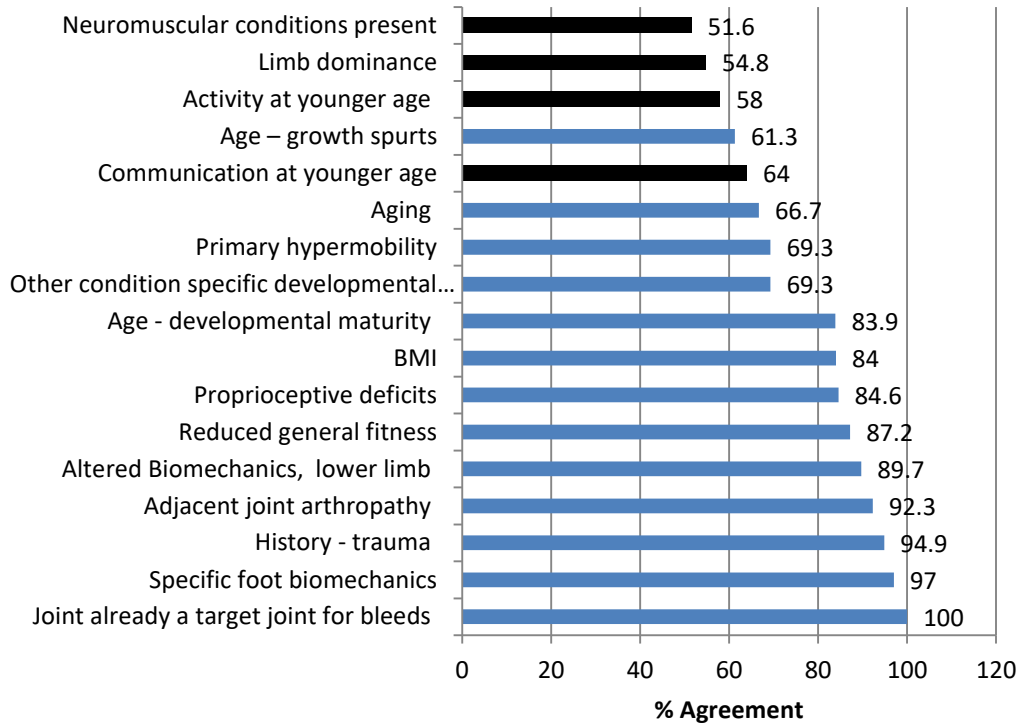
phenotype and their annual factor replacement usage is low (Aznar et al 2000) whereas some patients with moderate haemophilia have a presentation similar to severe haemophilia requiring regular prophylaxis (Den Uijl et al 2012). All bleeds are thought to cease if the levels are maintained at around 10 % (Den Uijl et al 2011a) although a lesser level of 5% could prevent most spontaneous bleeds. Moreover, there is a difference in clinical presentation of haemophilia in that the level of circulating factor level is not fully predictive of clinical presentation. To achieve this goal the two major difficulties that need to be surmounted are the frequency of self-infusions and the cost of the replacement therapy.

Whilst there has been and continues to be research into haematological aspects underlying this variability in presentation and response to treatment, the role of non-haematological factors that may impact on clinical presentation and outcomes of regular prophylaxis is poorly defined. Further, there is poor distinction between factors that initiate and perpetuate a bleed and arthropathy. It is conceivable that factors could affect either or both, and management would need to be appropriately tailored for the best outcomes in a given patient.

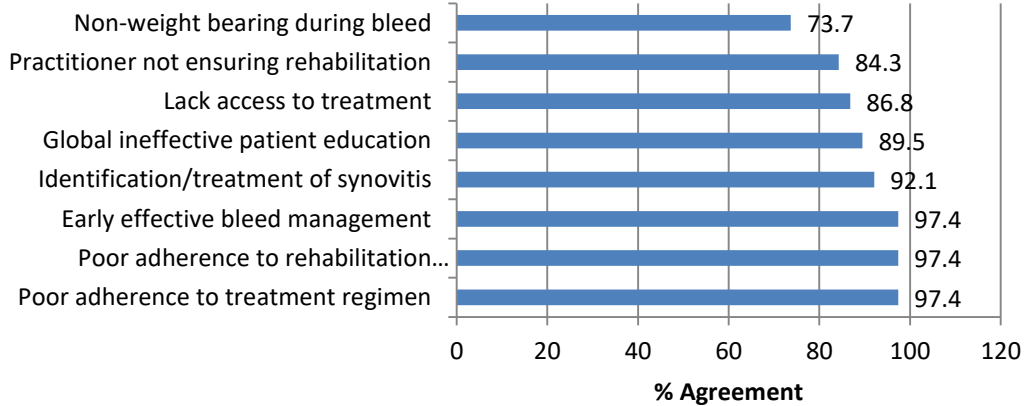
2.2 Delphi Survey

To achieve the haemophilia community's aim of no or minimal joint damage that is cost effective, an understanding of all aspects of the pathophysiology of arthropathy and management of haemophilia is important. To this purpose the research group carried out a Delphi survey to gather expert opinion about non-haematological factors that could potentially influence the development of haemophilic arthropathy. The Delphi method is of particular value for achieving a consensus of expert opinion on any given topic where it is considered that there is too much, too little, uncertain or contradictory information. The anonymous nature of the feedback and use of rating scale helps decrease bias and the use of a facilitator decreases ambiguity. The survey had 3 iterations and 41 factors reached consensus, which were grouped into 4 categories. These results show that the group of 31 experts on the multi-professional, international Delphi panel concur that whilst the severity and management of haemophilia is key, multiple factors influence the development and outcomes in haemophilic arthropathy. The 4 categories were (a) musculoskeletal intrinsic (b) compliance, education and non-haematological management (c) extrinsic factors affecting physical health (d) haematological management. The suggested factors under each category are presented below. For a factor to be included for consideration in future study, 60% of the panel had to vote for it as being important. Items in black were rejected.

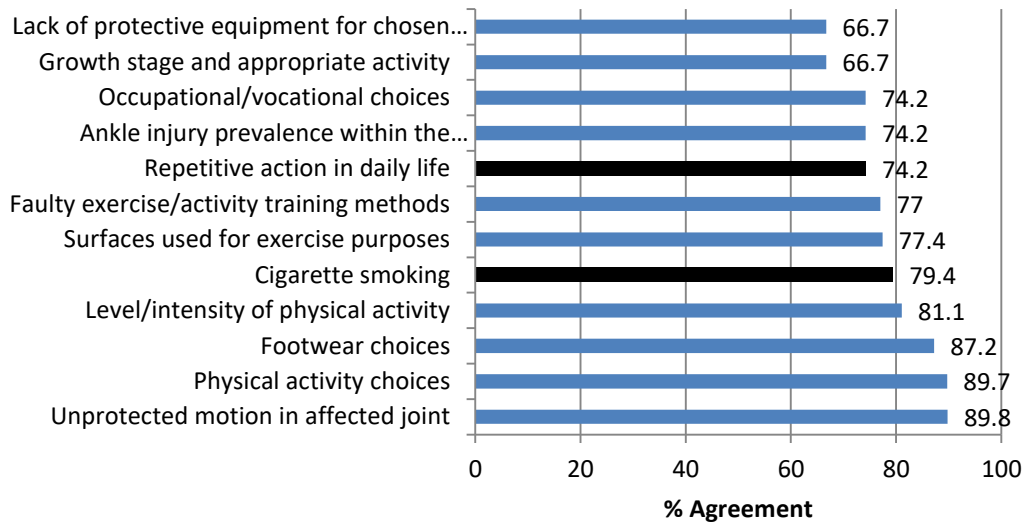
Musculoskeletal Intrinsic Factors



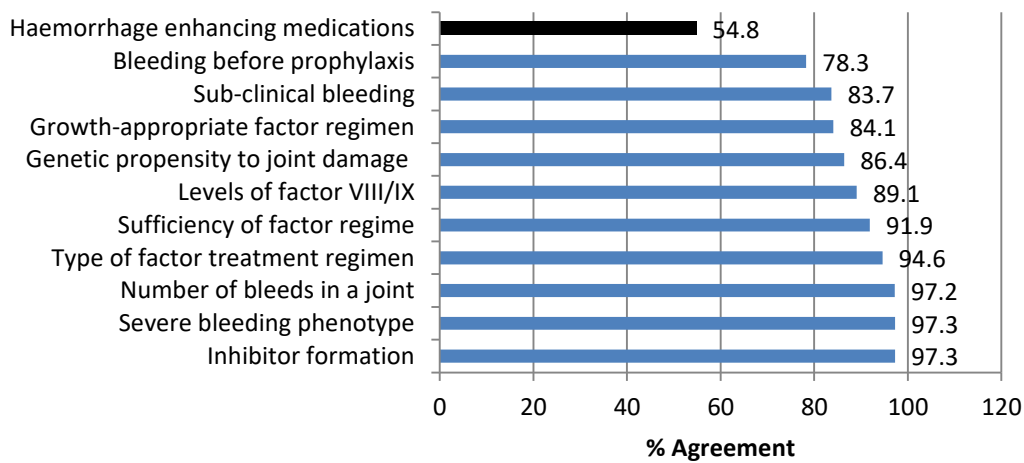
Compliance, Education & Non-Haematology Management



Extrinsic Factors Affecting Physical Health



Haematology Intrinsic Factors



2.3 Rationale for study

The results of the Delphi survey suggest that development of haemophilic arthropathy is multifactorial and it is reasonable to consider that the haemophilia exists within a wider context of factors with the potential to contribute to arthropathy development as demonstrated in other arthropathies. Empirical observation has suggested that there are differences in musculoskeletal and other factors present in some PWH. It is currently unknown which of these, if any, has the capability to influence the development of haemophilic arthropathy. The current evidence base therefore does not permit screening for these factors with the purpose of prevention of arthropathy. This is important as many may be altered by simple interventions such as specific exercise training which would ameliorate their effects. Identification of non-haematological factors would also allow the recognition of those with an inherent increased risk of developing haemophilic arthropathy allowing tailoring of their factor replacement regimen to reduce this risk.

Since the advent of prophylaxis, joints are preferentially affected in this order: ankle, knee and elbow (Aznar et al 2000). Previously, the knee was most commonly affected. The change in order may reflect normalisation in activity levels in people with haemophilia on prophylaxis and home treatment allowing them to be more active. Logically, this normalisation may also be reflected in types of injury sustained. Ankle sprain is one of the most commonly sustained injuries. Meta analysis indicates that males sustain 6.94 sprains per 1,000 sport exposures. Children sustain more than adolescents, who sustain more than adults (2.85 vs 1.94 vs 0.72 per 1,000 sport exposures) (Doherty et al 2014). 5000 ankle sprains are reported per day in the United Kingdom (UK) and lateral ankle sprain represents around 80 - 85% of all ankle injuries (O'Loughlin et al 2009). It is likely that many more go unreported as they are often minor injuries not requiring hospital attendance. It should also be noted that not all sprains are sport related. Ankle sprain generally affects the lateral supporting ligaments and only at the most severe grades is considered to affect the joint capsule (structure thought to be the source of bleeding in haemophilic ankle joint bleeds) (Taunton et al 1996). Despite the high incidence of ankle sprain, it has been noted that ankle joint cartilage appears to be generally resistant to symptomatic osteoarthritis (which has similarities in presentation to haemophilic arthropathy) and degeneration that does occur appears not progress to a symptomatic state (Kuettner & Cole 2005). This is in marked contrast to the knee where ligamentous damage has been linked to latent and symptomatic degeneration of the joint (Leys et al 2012).

Because of this relative joint protection even with high incidence of local trauma, non-haematological factors identified to influence the development of ankle haemophilic arthropathy will be of high importance, potentially having greater impact in other joints where cartilage is more susceptible. Therefore, patients with ankle arthropathy with relative sparing of the knee joint as identified by a physical assessment were considered the ideal group to determine the influence of non-hematological factors.

The suggested factors, in particular intrinsic musculoskeletal factors, were discussed in terms of feasibility and potential for influencing arthropathy development. Several extrinsic factors will be explored and data will be gathered on haematological factors for the final analysis.

To date a report of the Delphi survey has been accepted for publication in the Haemophilia Journal. Established and novel assessment tools and questionnaires have been piloted for feasibility. The current proposal is for a cohort study of patients with and without haemophilia, with and without ankle joint disease with a view to identifying factors that influence development of haemophilic arthropathy.

2.4 Assessment Tools and Limitations

The factors to be addressed and assessment tools are listed in the table below.

Table 1.1 DELPHI FACTORS TO BE ADDRESSED IN STUDY	
Musculoskeletal Intrinsic	
Factor	Measure
Adjacent joint arthropathy	HJHS & HEAD-US
Age - developmental maturity	Physical Activity Questionnaire
Age – growth spurts	Physical Activity Questionnaire
Altered Biomechanics of lower limb affecting the foot/ankle	Star Excursion Balance Test, Single Leg Squat Test,
Joint already a target joint for bleeds	HJHS & HEAD-US
History - trauma	Physical Activity Questionnaire
Primary hypermobility	Brighton Criteria, 5-Point Hypermobility Questionnaire, FDQ-9 (dyspraxia questionnaire)
Proprioceptive deficits	Star Excursion Balance Test, Timed Single Leg Stance
Reduced general fitness	Grip test, Star Excursion Balance Test, Tecumseh Step Test.
Specific foot & ankle biomechanics and anatomy	Ankle dorsiflexion, Great toe extension, Foot Posture Index, Subtalar inversion/eversion
Weight/BMI	BMI
Extrinsic Factors Affecting Physical Health	
Factor	Measure
Surfaces used for exercise purposes	Physical Activity Questionnaire
Faulty exercise/activity training methods	Physical Activity Questionnaire

Growth stage and appropriate activity	Physical Activity Questionnaire
Lack of protective equipment for chosen activity	Physical Activity Questionnaire
Level/intensity of physical activity	Physical Activity Questionnaire
Occupational/vocational choices	Physical Activity Questionnaire
Physical activity choices	Physical Activity Questionnaire
Compliance, Education & Non-Haematology Management	
Factor	Measure
Poor adherence to rehabilitation programmes	Physical Activity Questionnaire
Haematology Intrinsic Factor	
Factor	Measure
Bleeding before prophylaxis	Medical Records
Number of bleeds in a joint	Medical Records
Levels of factor VIII/IX	Medical Records
Inhibitor formation	Medical Records
Sufficiency of factor regime	Medical Records
Type of factor treatment regimen	Medical Records
Severe bleeding phenotype	Medical Records

Haemophilia joint health score (HJHS) will be used to identify ankle arthropathy when for screening eligible patients. Within the UK and many other countries, the health of the ankle, knee and elbow joints is commonly monitored using the paediatric and adult versions of the haemophilia joint health scores (HJHS) (Feldman 2011; Hilliard et al 2006) as routine. However the adult version is yet to be fully validated with reference to sensitivity for identifying joint disease and monitoring progression.

The HJHS has good construct validity, but the literature on its sensitivity and specificity for early joint damage is limited. It has been shown to be not sensitive to early joint disease in children, with a weak correlation with magnetic resonance imaging (MRI) ($r = 0.26$ $P = 0.02$) (Manco - Johnson et al 2007). Additionally, a prospective study found that 26/101 joints in 26 participants with positive MRI scores reported no loss of function as determined by the HJHS, and five joints with no change on MRI showed some minimal change on HJHS (Median of 1, IQR 1 – 3) (Den Uijl et al 2011b). Further analysis of the HJHS scores on 101 knee and ankle joints in 26 people with haemophilia A and limited arthropathy identified on MRI, shows that HJHS has a sensitivity and specificity of 35.71% and 83.05% respectively for identifying limited arthropathy.

The gold standard for identifying early arthropathy continues to be MRI, but it is not conducive for routine clinical use as a screening investigation, both due to time and expense. Ultrasound (US) has the potential to bridge the gap between the expense of MRI and the reported lack of sensitivity of the HJHS. Several studies have evaluated the sensitivity of US compared to MRI with respect to evaluation of haemophilic arthropathy. US results were comparable to MRI for detecting joint bleeds, synovial hyperplasia and joint erosions (Sierra Aisa et al 2014). It has also been noted to detect subclinical joint changes in severe haemophilia (Di Minno et al 2013). Recently a score has been developed and piloted called the **Haemophilia Early Arthropathy Detection with Ultrasound Score (HEAD-US)** designed as a screening and monitoring tool with increased sensitivity for early joint disease. It has been designed specifically with ease of use in mind and may be the suitable as it is both time and expense contained. Overall inter-observer agreement (reporting of the US) was reported as excellent ($k=0.71 - 0.81$) and the overall intra-observer agreement was good to excellent ($k=0.68 - 0.78$) (Martinoli et al 2013).

Ideally it could be argued that patients should be screened with an MRI before inclusion into the study, but cost and patient acceptability severely limit its use in this context. Whilst the HJHS is not sensitive to early joint damage, the specificity ensures that patients included into the study will show joint damage with imaging, hence for this multicenter study the HJHS will be used for both screening and assessment of joint damage. The US could be considered as the initial screening tool, but across UK there is limited expertise. Furthermore patient acceptability and practical implementation could threaten patient recruitment. US in this study has been included as adjunctive tool as it has potential to increase the number of patients with early joint damage increasing the power of the study to identify significant factors. To ensure that the group of haemophilia patients with no evidence of joint damage is not disproportionately affected by the use of US, recruitment will be spread across the severity in the context of data presented by Den Uijl et.al (2011a). It is important to acknowledge that whilst the HJHS may not be sensitive for detecting early joint damage, our data shows it has strong correlation ($r>0.9$) to Haemophilia Activities List, which is a functional assessment of the patients joint status. The debate on functional or radiological outcome as the ideal outcome in haemophilia treatment is yet to be had, hence the use of both clinical and radiological score.

Following the successful conclusion of this study, it is hoped that targeted interventions may be prospectively initiated and their impact on factors such as quality of life, number of bleeds, factor usage and joint health will be investigated.

3. Study Aim

The overall aim of this programme of work is to assist health care professionals to be able to better target the management of PWH in order to prevent or ameliorate the destruction of joints due to haemophilic arthropathy.

4. Study Design

4.1 General Design

This is a between groups correlational study that involves assessing four groups of people: PWH - with and without established mild to moderate ankle joint disease or a tendency to bleed into the ankle joint, PWH with no joint disease, non-PWH with mild to moderate ankle joint disease and healthy controls, using clinical tests and surveys that are not part of routine haemophilia clinical care, in order to identify any links between tested factors and the presence of haemophilic arthropathy.

US assessment will be undertaken by practitioners who have undergone a calibration exercise in collaboration with HEAD-US development group. In all patients standard images will be stored for subsequent review. It is anticipated that only a two thirds of haemophilia patients will be able to have an US performed due to issues related to access and competency. At the time of the US of the ankles opportunity will be taken to scan the other joints as part of evaluation of adjacent arthropathy and for evaluation of agreement between the haemophilia joint health score and the HEAD-US haemophilic arthropathy ultrasound evaluation score.

4.2 Primary Objective

- Evaluate the influence of musculoskeletal factors on the development of ankle arthropathy in people with severe or moderate haemophilia to identify patients with a high risk of arthropathy phenotype.

4.3 Secondary Objectives

- Understand the relative contribution of musculoskeletal factors to the development of haemophilic arthropathy in those that are at a high risk of developing the condition to enable personalised interventions.
- To explore the influence of extrinsic factors affecting physical health that can influence the development of haemophilic arthropathy.
- Evaluate the agreement between the HEAD-US ultrasound scoring system and the HJHS in identify joint damage.

4.4 Primary End Points

- Univariate analysis will be carried out on measures of strength, balance, co-ordination, flexibility and fitness (aspects of musculoskeletal health) to identify factors with significant correlations between the variable and haemophilic arthropathy, where the latter is identified by HJHS score and HEAD – US score.
- Individual measures are listed in 5.5 below.

4.5 Secondary End Points

- Variables reaching significance will be entered into multivariate regression analyses in order to assess their relative influence on haemophilic arthropathy development.
- Parameters of exercise choices will be considered as co-variables in the analyses.
- Bland-Altman Agreement Test will be applied to the HEAD-US and HJHS scores to evaluate their agreement.

4.6 Study Group Composition

180 participants will be recruited into 4 groups:

1. Mild, moderate or severe haemophilia with ankle joint disease and no/minimal knee disease (N=60)
2. Mild, moderate or severe haemophilia with no history of joint disease spread across severity (N=60)
3. Non-haemophilic ankle joint disease (N=30)
4. Healthy control group (N=30)

4.7 Sample size calculation

Dominant ankle arthropathy with relative sparing of knees is the study group that will yield results of interest in relation to the primary objective. Unfortunately this is a relatively small group as primary prophylaxis has been the standard of care for the last couple of decades only. A decision was taken to include multiple groups to account for known variables like haemophilia and common musculoskeletal conditions like hypermobility. This allowed an increased sample base for recruitment. Age-matching was considered but due to the small sample size, multiple procedures, and patients with non- haemophilic joint disease present at a later age, this is not feasible across all groups.

The uneven number of participants in each group must be considered in light of study feasibility, including rationale for inclusion and eligible pool of patients. A control group of a different size is commonly seen in research practice, unless the sample size is very small at less than 30 to 40 when the controls tend to be age matched to the study population. Published studies of degenerative ankle joint disease with single pathology often tended to have sample sizes of less of 20 to 30 (Gross & Marti 1999; Niek van Dijk et al 1995; Valderrabano et al 2006). As the aim of the current study is to understand the influence of intrinsic musculoskeletal and exercise factors on the

ankle arthropathy, systemic causes of arthropathy have been excluded from the non-haemophilia arthropathy group and a sample size in keeping with the published literature has been included. Finally, as some of the variables under investigation have a population prevalence across all the groups, it is not necessary to maintain the control group (which is effectively controlling for the musculoskeletal variables) at the same size.

When undertaking a study of this design it is necessary to predict the number of variables that will achieve or come near significance. For the purposes of this investigation a study of a similar design was consulted along with taking statistical advice. Hubbard et al. (2007) investigated factors that might influence the development of chronic ankle instability starting with 31 variables and after univariate analysis included 13 items in their discriminant regression analysis. Many of the variables are the same as in this study. As the variables in this study are not all ratio data, logistic regression analysis is most appropriate. This analysis requires ten participants for each potentially significant variable to be included and which would be less than 180, taking into account the above study. In the event that the number of variables identified are more than 15 that it is reasonable to include only the top 10 to 13 factors identified in univariate analysis into the final regression analysis. Moreover as for some variables multiple testing procedures have been included, the variable can be included in regression once and each testing method substituted to see which method is the strongest indicator.

4.8 Inclusion and Exclusion Criteria

Inclusion criteria			
All Groups			
Participant is willing and able to give informed consent for participation in the study			
Male, aged 12 to 50 years. Age is adequate for maturation of the foot into adult posture & of the ankle/foot for adult gait pattern, proprioceptive ability and passing of transient childhood hypermobility. (Donatelli 1990; Skeith et al 2010). After 50 years of age, balance ability is known to reduce and would bias results.			
Haemophilia joint disease	Haemophilia no joint disease	Ankle joint disease	Controls
Haemophilia A or B with predominant ankle joint problems: bleeding into the ankle joint, pre-clinical, mild or moderate signs of arthropathy able to perform a step-up to a 24cm step and with a functional gait.	Haemophilia A or B with healthy limb joints. 50% of the patients will have a factor VIII or IX level of >10%.	Presenting with ankle joint disease: chronic ankle instability & OA.	No lower limb joint disease or history of major trauma to the lower limb joints.
Knee arthropathy may be present at grade 1, must be less symptomatic than the ankle. Presenting without functional limits.			

Exclusion Criteria			
The participant may not enter the study if ANY of the following apply			
All Groups			
Inability to perform step up to a 24cm step & ankle motion below that necessary for normal gait.			
A history of unstable hypertension or cardiac disease or use of beta blockers.			
Person has a resting heart rate of over 100bpm or a systolic blood pressure of 150mmHg on day of testing (Reilly & Tipton 2010).			
Any lower limb injury in the last 6 months.			
Any ear or eye condition or injury, or any history of head injury that could affect balance.			
Unable to provide informed consent/assent.			
Unable to complete surveys in English.			
Haemophilia joint disease	Haemophilia no joint disease	Ankle joint disease	Controls
Person with an actively bleeding joint may not be seen on the day, but could be seen at another time.		Open surgery to the ankle or knee joints such as arthroplasty.	
Presence of knee arthropathy with marked functional limitations.		Systemic cause of arthropathy.	
Open surgery to the ankle or knee joints such as arthroplasty.			

5. Conduct of Study

5.1 Sites and Logistics

This is a multi-centre study over two years. The Katharine Dormandy Haemophilia Centre (KDHC) will act as the hub for the study. The University of Brighton will sponsor the study with study funds managed by the Royal Free London NHS Trust who will disseminate funds to other centres. It is anticipated that recruitment will take in the following centres.

- KDHC, Royal Free London NHS Foundation Trust (all groups)
- Guy's & St Thomas' Centre for Haemostasis and Thrombosis, London (PWH)
- Oxford Haemophilia & Thrombosis Centre, Churchill Hospital (PWH)
- Haemophilia, Haemostasis and Thrombosis Centre, Basingstoke and North Hampshire Hospital (PWH)
- Royal London and Barts Haemophilia Centres, London (PWH)
- Homerton University NHS Foundation Trust (Non-haemophilic arthropathy)

The co-principal investigator will operate using a Research Passport. This is a system for issuing honorary contracts for researchers wishing to undertake research in the National Health Service (NHS). This provides evidence of pre-engagement checks undertaken on the researcher in line with NHS Employment Check Standards. It also provides NHS to NHS sharing arrangements for staff wishing to carry out research outside their home trust. This will ensure ease of access to participating centers and facilitate training of the physiotherapists on the protocol.

This study will be eligible for National Institute of Health Research (NIHR) portfolio raising the profile of the study and will facilitate recruitment at centers other than stated above. NIHR portfolio consists of high quality clinical research studies that are eligible for support from the NIHR Clinical Research Network in England, and requires rigorous peer review for adoption. The time line for this study is shown as appendix 29.

5.2 Recruitment and screening

PWH and non-PWH arthropathy participants who fulfill the inclusion criteria will be recruited from the participating haemophilia centres and associated NHS trusts after screening and identification from medical records and will be approached by a member of the direct health care team (doctor, physiotherapist or nurse) abiding by the principals of research governance. Non-haemophilia ankle joint disease group and control group participants will be recruited from the host NHS trusts, local advertising and local schools and sports clubs if necessary. The background to the study, the procedures, benefits and risks of the study will be explained to the potential participant. It will be made clear that taking part is voluntary and that the participant can choose to withdraw at any time. Good research practice requires that participants are given a minimum of 24 hours to consider their participation. For those under eighteen years, age appropriate information will be provided. Participants, and/or parents/guardians where applicable, must provide consent/assent before any participation.

5.3 Study procedure – Medical notes review

Medical records will be reviewed to document the details of the haemophilia diagnosis and management. This is detailed in Appendix 1. Some of these items will be included in the multivariate data analysis such as: age starting prophylaxis, haplotype/genetic mutation and factor level as covariates.

5.4 Study procedure – Physical examination and surveys

Participants will undergo a series of clinical tests and surveys. Although most clinical tests have been listed as not part of routine care they are standard musculoskeletal tests and the participant may at some point have undergone one or more as part of an individualized care programme. The

order of testing has been designed to minimise physical stress and is detailed in the Table below.

The procedure of individual clinical tests is described fully in Appendices 2 – 11. Surveys are detailed from Appendices 12 – 16.

- Yellow – for inclusion in regression analysis.
- Grey – screening test not for inclusion in regression analysis.
- Blue – exploratory analysis

Test or Survey	Measuring	Approximate Duration	Routine Care?	Conducted By & Level of Effort
Haemophilia Joint Health Score (ankle, knee, gait)	Evaluates health of the joint.	5 minutes	Yes	Physiotherapist. Minimal effort.
Chronic Ankle Instability Screen	Determines Group 3 matching inclusion criteria	5 minutes	No	Minimal effort. Recruitment person.
Physical Activity Questionnaire	Levels & types of exercise undertaken. Occupation. Compliance with rehabilitation.	20 minutes	No	Novel questionnaire designed in response to the Delphi survey. Sedentary.
Basic Measures (height, weight, leg length & foot length)	BMI	10 minutes	Yes – partly for BMI purposes	Other measures are for use in later test: Star Excursion Balance Test. Minimal effort.
Anterior Draw Test	Assesses stability of the ankle joint.	1 minute	No	By physiotherapist. Passive test. Person long-sitting.
Great Toe Dorsiflexion Range	Assesses available motion in the great toe.	3 minutes	No	By physiotherapist. Passive test. Person long-sitting.
Subtalar Inversion/Eversion Range	Assesses available motion in the subtalar joint.	5 minutes	No	By physiotherapist. Passive test. Person prone lying.
Ankle Lunge Test	Assesses available motion in the ankle joint complex.	4 minutes	Yes	By physiotherapist. Minimal effort in standing.
Star Excursion Balance Test	Dynamic balance, co-ordination and	10 minutes	No	By physiotherapist. Moderate effort in standing.

	lower strength.			
Foot Posture Index	Static foot posture.	2 minutes	No	By physiotherapist. Sedentary standing.
Timed Single Leg Stance Test	Static balance.	5 minutes	No	By physiotherapist. Minimal effort in standing.
Brighton Criteria	Presence of benign joint hypermobility syndrome	5 minutes	No	Survey in sitting. Sedentary.
5-Point Hypermobility Questionnaire	Presence of joint hypermobility	1 minute	No	Survey in sitting. Sedentary.
FDQ – 9 (dyspraxia questionnaire)	Presence of dyspraxia.	1 minute	No	Survey in sitting. Sedentary.
Single Leg Squat Test	Assesses lower quarter control.	5 minutes	No	By physiotherapist. Moderate effort in standing.
Calf Strength Test	Assesses plantarflexor muscle strength.	5 minutes	No	By physiotherapist. Moderate effort in standing.
Human Activities Profile	Measure of general fitness	10 minutes	No	Survey in sitting. Sedentary.
Grip Test for Strength	Indirect measure of thigh muscle strength.	5 minutes	No	By physiotherapist. Moderate effort in sitting.
Tecumseh Step Fitness Test	Assesses aerobic fitness.	5 minutes	No	By physiotherapist. Moderate effort in standing.
Foot & Ankle Ability Measure	Assesses functional level of the foot	5 minutes	No	Survey in sitting. Sedentary.
Total time		Max 1.45 hours		

Ultrasound evaluation of arthropathy* *may occur on a different day if necessary	Evaluates health of the joint.	10 minutes	No	By radiologist or physiotherapist to indicate the health of the joint. Non-weightbearing, person long-sitting.
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Physiotherapists at all participating centres will be fully trained in the test procedures and will be provided with the necessary equipment and support by the co-principal investigator. It should be noted that the majority of the tests are standard practice in musculoskeletal assessment and will be familiar to physiotherapists. A step-by-step procedures book will be provided. This training will take place at least four weeks in advance of data collection to allow for practice.

The HEAD-US ultrasound score will be performed only by clinicians who have undergone specific training in the use of the tool and have completed a calibration exercise. It is anticipated that all scans will be completed by musculoskeletal specialist consultant radiologists or the co-principal investigator, a physiotherapist, after being deemed competent by the consultant sonographer.

5.5 Study Procedure – Interview

A subset of the haemophilia groups will be invited to take part in an interview based on the answers to the activity questionnaire. It will be a purposive sample. This will be a semi-structured interview with questions derived from the questionnaire responses with the intention to gain in depth understanding of reasoning behind exercise and physical activity choices. Therefore the precise interview structure is not presented within this document. A maximum of five questions are anticipated and an approximately 30 minute telephone interview by appointment on a different day to the assessment. Up to 15 participants interviews will be sought.

6. Statistical Analysis

Sample size calculations have not been formalised for this type of correlational study where multivariate regression analysis is intended however there is a “rule of thumb” whereby 10 participants are recommended per variable to be entered into the analysis. As the study is exploratory in nature population prevalences of the potential influential factors is not relevant. In consultation with a biostatistician and using a similarly structured study as a basis (Hubbard et al 2007), it has been recommended that a cohort of 180 will suffice. For more detail please see section 4.7 above. Descriptive statistics will be used to describe the participants of the study. Statistical support will be available from Dr Alfonso Iorio (McMaster University) who will particularly assist with the regression analysis models.

6.1 Group comparisons: Involved versus Sham-Involved

Where data is of normal distribution, it is proposed to use 4 x 2 mixed model ANOVAs. Where non-normality is identified, items will either be transformed or the appropriate non-parametric test will be used such as Friedman’s test. Items identified as being significantly ($P \leq 0.05$) different (group by

side interaction or group main effect) will be entered in a series of discriminant regression analyses. As this study is exploratory in nature, any variable nearing significance will also be included.

6.2 Group comparisons of symmetry indices

Side-to-side differences will be examined within subject in the haemophilic arthropathy group. A symmetry index will be calculated as follows:

Symmetry index = (Involved ankle variable/Uninvolved ankle variable) * 100

Indices less than 100% indicate a deficit in the involved side and indices greater than 100% indicate that the involved side scored higher. Independent t-tests will then be calculated for all indices.

Variables demonstrating significant ($P \leq 0.05$) differences will be entered into a series of discriminant regression analyses.

6.3 Comparison of ultrasound and haemophilia joint health score for the ankle

A Bland – Altman Agreement test will be applied. Secondary univariate analysis will be undertaken between the HEAD-US score and the measured variables. This may be carried out either as an aggregate score as some measured variables consider the whole body or using only the ankle component. The type of univariate analysis will be dependent on the normality of data distribution.

6.4 Analysis of Interview

Qualitative thematic analysis techniques (Braun & Clarke 2006) will be used to interpret the meaning behind the participant's experience of exercise with haemophilia. Appropriate support with this aspect of the analysis will be sought in terms of advice, peer support and additional training if indicated.

7. Data Handling and Record Keeping

Information about patients will be kept confidential and managed in accordance with Trust Data Protection Guidance, which incorporates the Data Protection Act of 1998. Data will be pseudoanonymised at the earliest opportunity and access to patient identifiable data will be restricted to the investigators and members of the direct health care team. Copies of consent forms, case record forms, and results will be filed in dedicated study folder and stored in a locked room dedicated for clinical trials and studies. Access to this information will be restricted to the investigators only.

All patient identifiable data will be stored on NHS computers and NHS approved devices in accordance with Trust Data Protection guidance. Data will be collated using databases held on the said password protected computers. Complete confidentiality will be maintained at all times. Only the investigating team will have access to the data.

8. Ethical Issues

The proposed study is non-interventional. The feasibility of the testing protocol has been piloted on lay volunteers and two people who meet Group 1 inclusion criteria. It was found that the proposed study is acceptable.

8.1 Safety

The proposed clinical assessments are considered to exert minimal physical strain on the individual and an inclusion criterion requires that any arthropathy present to be pre-clinical or of mild presentation, and therefore it is considered that the participants are at low risk of injury. Heart rate and blood pressure will be checked on the day of study in order to ensure it is within acceptable ranges (see exclusion criteria). In order to ensure safety, where appropriate participants will be asked to ensure that they have prophylactic factor cover for the duration of the assessment. Subjects presenting with an overt ankle bleed on the day of assessment will be excluded from the trial at that time.

8.2 Age & Consent

As the study requires a mild presentation, it may require a younger participation group. It is the intention to recruit enough adult participants, however, if it becomes apparent that not enough adults are available, then further care will be taken with consenting potential participants under 18 years of age, ensuring that participant and guardian know the full extent of the study being proposed. Appropriate age-related information will be made available. The minimum age for participants is 12 years of age which requires information measured at grade level 8 on the Flesch-Kincaid Grade level reading ease score or a Flesch Reading Ease level of around 60% - 70% (Scott 2012). The paediatric information sheet below measures at grade 7.4 and 72%.

9. Funding

This study has received funding from the Investigator-Initiated Research programme, an unrestricted educational grant from Pfizer Ltd of Ramsgate Road, Sandwich, Kent CT13 9NJ.

10. Sponsor

The University of Brighton will sponsor this study. NHS Indemnity will apply for this study.

11. Publication Plan

The results of the study will be presented internally, and at National and International meetings and in peer-reviewed journals. These might include: the World Congress of Physical Therapy; Chartered Society of Physiotherapy Congress musculoskeletal programme; World Federation of Haemophilia Conference; and Haemophilia Journal.

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PLEASE NOTE FOR PURPOSES OF ATTACHMENT TO THE THESIS ALL APPENDICES
DETAILED IN STUDY METHODS HAVE BEEN REMOVED BUT ARE INCLUDED IN THEIR OWN
RIGHTS ELSEWHERE.

E Appendix 14 Case Control Study Funding Letter



May 14, 2014

Dr P Chowdary,
Katherine Dormandy Haemophilia Centre,
Royal Free Hospital,
Pond St,
London
NW3 2QG

- Re: Pfizer Reference # **WI189942**
External Reference #

Dear Dr Chowdary,

The Haemophilia IIR Grant Review Committee has reviewed your proposal, Role of Non-Haematological Factors on the Development of Joint Disease in Haemophilia_ A Correlational Cohort Study. and is pleased to inform you that Pfizer is interested in supporting your research with funding and/or drug.

The total amount of funding you requested is £224,640 GBP.

Please complete and return the accompanying Site Information Sheet to begin the contracting process. For those studies being conducted in the United States and Puerto Rico where funding is provided, a completed IRS Form W-9 is required.

Pfizer support is contingent upon the receipt of:

- Final research protocol*
- IIR Agreement executed between Pfizer and your institution
- IRB/IEC approval (as appropriate)
- Regulatory response (see enclosed guidelines)

*Please be aware that if the research described in your final protocol is materially different from that presented in your original proposal, then Pfizer reserves the right to reconsider its support.

If you have not obtained IRB approval and/or executed the IIR Agreement with Pfizer **within six (6) months** from the date of this letter, then funding for your grant cannot be guaranteed. Although this letter signifies Pfizer's intention to support your proposal, Pfizer is not committed until an agreement has been fully executed.

To ensure that the Pfizer safety and pharmacovigilance obligations are met, Serious Adverse Events (SAEs) must be reported to Pfizer for all clinical studies using a Pfizer product. In addition, for IIR studies using a Pfizer device or Pfizer product packaged with a device, reportable events include not only SAEs but Device Incidents and Device Near-Incidents. The reporting of these events to Pfizer does not relieve you or your institution of the responsibility to report any such event to the FDA or to the local regulatory authorities that govern your institution. Please review the accompanying IIR SAE training materials carefully to fully understand your Pfizer Safety reporting obligations.

Pfizer recognizes that carefully conducted clinical trials are the fastest and safest way to find treatments to improve health. As such, Pfizer encourages you and your institution to add this study to the FDA's www.clinicaltrials.gov database. Pfizer recognizes that the availability of clinical trial listings and results are critical to the communication of important new information for the medical profession, patients, and the public.

If you have questions, please contact me on 0776 8548723.

We look forward to working with you.

Yours sincerely,

A handwritten signature in black ink that reads "Lisa Young". The signature is written in a cursive, flowing style.

Lisa Young

Senior Medical Scientific Relations – Haemophilia – Pfizer UK

lisajayne.young@pfizer.com

E Appendix 15 Case Control Study Information Sheet Adult, Haemophilia Control

**University of Brighton
Centre for Clinical Research**

Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia. Participant Information Sheet for Adults Group 2 Haemophilia with No Joint Problems

1 Study title

Evaluation of the Effect of Musculoskeletal Factors on the Development of Joint Disease in Haemophilia.

2 Invitation

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

3 What is the purpose of the study?

In this study we are hoping to find out whether things other than haemophilia affect how much or how often someone bleeds into their ankle joint. We have designed a new assessment tool to help us determine this which consists of clinical tests and surveys. We are asking you to undergo the assessment to help us determine this.

4 Why have I been invited?

You have been invited to take part in this study because you have haemophilia with no history of joint disease. Unfortunately you will not be able to take part if you have had any major surgery or procedures on your ankles or knees or if you have any condition that might affect your balance. Also, should you decide to take part, your visit may be postponed if you have experienced an ankle or knee bleed within 6 weeks of the visit date or if one is present on day of testing.

5 Do I have to take part?

It is up to you to decide; it is totally voluntary. We will describe the study and go through this information sheet, which we will then give to you. Please take it away and decide whether you would like to help us in this research. If you decide to take part, then please read and sign the attached Consent Forms and return one to us in the envelope provided, keeping a copy for your own records. You are free to withdraw at any time, without giving a reason. You will not be affected in any way by a decision not to take part or withdraw.

6 What will happen to me if I take part?

You will be asked to attend a treatment centre on one occasion. You will be asked to answer some questions and also to perform some simple clinical tests. An ankle assessment that you have already experienced as part of your normal care will be repeated followed by a set of clinical tests used to measure aspects of your strength, flexibility, balance and fitness. Depending on your condition, you may or may not have done these tests before. For one test, we will video you performing a movement for analysis after the session; these images will be deleted immediately after grading. The questionnaires will be alternated with the clinical tests to allow you to rest in between. The questions will also be about flexibility and exercise. We expect that this whole process will take no longer than 1.45 hours in total. Depending on your answers to the exercise questionnaire, we may contact you to do a 30 minute follow up interview to make sure we have learned and understood as much as possible. This interview would be recorded. We would also like to look

at your medical records to access data about your haemophilia so that we do not have to use your time to ask you. Please inform us if you do not want us to do this.

Also, whilst we are confident that the clinical tests being used are low risk, we would ask that if you normally use prophylaxis before exercise that you ensure that you have used some before taking part. We will check your blood pressure and heart rate on the day of testing to make sure you are fit enough to take part. We would also ask that you do not partake of alcohol for 24 hours prior to the study as this may have a residual effect on your ability to balance.

Please bring shorts and trainers with you.

7 What are the possible disadvantages and risks of taking part?

If you have used prophylaxis it will offer some protection against sustaining a bleed. I will ask whether you have used prophylaxis before we begin. If you have not and normally would, we may consider re-arranging the appointment. Please inform me immediately during the testing if you should feel any discomfort or are concerned in any way.

8 What are the possible benefits of taking part?

There may not be an immediate benefit to you in taking part in this research, but the information will allow us to improve our understanding of the things that contribute to the development of ankle joint disease in people with haemophilia.

9 What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might have suffered can be addressed by contacting my supervisor, Dr Pratima Chowdary. Alternatively you can contact the Patient Liaison and Advice Service (PALS) on* For further contact details see the bottom of the information sheet

10 Will my taking part in the study be kept confidential?

The information you provide during the assessment and information about your haemophilia will be entered on an electronic spreadsheet which will be stored on an encrypted NHS computer. You will be referred to by a reference code on the spreadsheet and no personal identifiable information will be stored. Only the researchers will be able to access this information. This information will be kept until the series of studies is completed when it will be destroyed, approximately 3 years. Copies of consent forms, case record forms, and results will be filed in a dedicated study folder and stored in a locked room dedicated for clinical trials and studies.

11 What will happen to the results of the research study?

This study is part of a PhD programme. The results of all the people taking part in the study will be analysed both by statistics and text exploration to see if we can establish any relationships between the things that we tested for and a person with haemophilia's tendency to develop ankle joint disease. As part of the study write-up anonymised direct quotes may be used. The results of this study will also be presented at National and International meetings and in peer-reviewed journals.

12 Who has reviewed the study?

This study has been reviewed and approved by the Faculty of Health and Social Science Research Ethics and Governance Committee, University of Brighton and the NHS Research Ethics Committee (London - Hampstead Area).

13 Contacts for further information

PhD Principal Investigator

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Tel: 020 7794 0500 ext. 35921
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Co-Principal Investigator (Clinical Supervisor)

Dr Pratima Chowdary
Consultant Haematologist
The KD Haemophilia centre & thrombosis unit
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p.chowdary@nhs.net

*Individual centres local office number to entered here.

E Appendix 16 Case-Control Study: Information Sheet Adult, Normal Volunteer

**University of Brighton
Centre for Clinical Research**

Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia.

Participant Information Sheet for Adults

Group 4 Healthy Ankles

1 Study title

Evaluation of the Effect of Musculoskeletal Factors on the Development of Joint Disease in Haemophilia

2 Invitation

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

3 What is the purpose of the study?

In this study we are hoping to find out whether things other than the presence of haemophilia, affects how much or how often a person with moderate or severe haemophilia bleeds into their ankle joint. Haemophilia (pronounced heem-o-feel-ee-a) is an inherited bleeding disorder affecting boys and men. Bleeds occur into their joints and in particular the ankle. This eventually causes irreversible damage. As we cannot cure haemophilia, we are trying to find other ways of preventing joint damage. In order to do this, we need to compare people with and without haemophilia who do and do not have a problem with their ankle joint(s). We have developed a new assessment tool to help us determine this which consists of clinical tests and surveys. No blood tests or injections are involved. We are asking you to undergo the assessment to help us determine this.

4 Why have I been invited?

You have been invited to take part in this study because you have no history of problems with your ankle joints. Unfortunately you will not be able to take part if you have had any major surgery or procedures on your ankles or knees, or if you have any condition that might affect your balance. Also, should you decide to take part, your visit may be postponed if you have experienced a new injury to your ankle within 6 weeks of the visit date or if one is present on day of testing.

5 Do I have to take part?

It is up to you to decide; it is totally voluntary. We will describe the study and go through this information sheet, which we will then give to you. Please take it away and decide whether you would like to help us in this research. If you decide to take part, then please read and sign the attached Consent Forms and return one to us in the envelope provided, keeping a copy for your own records. You are free to withdraw at any time, without giving a reason. You will not be affected in any way by a decision not to take part or withdraw.

6 What will happen to me if I take part?

You will be asked to attend a treatment centre on one occasion. You will be asked to answer some questions and also to perform some simple clinical tests. The clinical tests will be used to measure aspects of your strength, flexibility, balance and fitness. The questionnaires will be alternated with the clinical tests to allow you to rest in between. The questions will also be about flexibility and exercise. For one test, we will video you performing a movement for analysis after the session; these images will be deleted after grading. We expect that this whole process will take no longer than 1.45 hours in total.

We will check your blood pressure and heart rate on the day of testing to make sure you are fit enough to take part. We would also ask that you do not partake of alcohol for 24 hours prior to the study as this may have a residual effect on your ability to balance.

Please bring shorts and trainers with you.

7 What are the possible disadvantages and risks of taking part?

The tests that you will be performing are considered to be low risk but please inform me immediately during the testing if you should feel any discomfort or are concerned in any way.

8 What are the possible benefits of taking part?

There may not be an immediate benefit to you in taking part in this research, but the information will allow us to improve our understanding of the things that contribute to the development of ankle joint disease in people with haemophilia.

9 What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might have suffered can be addressed by contacting my supervisor, Dr Pratima Chowdary. Alternatively you can contact the Patient Liaison and Advice Service (PALS) on 020 7830 2174. For further contact details see the bottom of the information sheet.

10 Will my taking part in the study be kept confidential?

The information you provide during the assessment and information about your haemophilia will be entered on an electronic spreadsheet which will be stored on an encrypted NHS computer. You will be referred to by a reference code on the spreadsheet and no personal identifiable information will be stored. Only the researchers will be able to access this information. This information will be kept until the series of studies is completed when it will be destroyed, approximately 3 years. Copies of consent forms, case record forms, and results will be filed in a dedicated study folder and stored in a locked room dedicated for clinical trials and studies.

11 What will happen to the results of the research study?

This study is part of a PhD programme. The results of all the people taking part in the study will be analysed both by statistics and text exploration to see if we can establish any relationships between the things that we tested for and a person with haemophilia's tendency to develop ankle joint disease. As part of the study write-up anonymised direct quotes may be used. The results of this study will also be presented at National and International meetings and in peer-reviewed journals.

12 Who has reviewed the study?

This study has been reviewed and approved by the Faculty of Health and Social Science Research Ethics and Governance Committee, University of Brighton and the NHS Research Ethics Committee (London - Hampstead Area).

13 Contacts for further information

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E Appendix 17 Case-Control Study: Information Sheet Young Person,

Haemophilia Ankle

**University of Brighton
Centre for Clinical Research**

Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia. Young Person's Information Sheet Group 1 Haemophilia with Ankle Problems

1 Study title

Evaluation of the Effect of Musculoskeletal Factors on the Development of Joint Disease in Haemophilia.

2 Invitation

We would like you to help us with some research. It is important that you understand what the research is for and what you would be asked to do. Please take time to read this information sheet carefully. Ask us if anything is not clear. Also ask if you would like more information. Take time to decide if you would like to take part.

3 What is the reason for the study?

In this study that is hoping to find out whether things other than your haemophilia affect how much or how often you bleed into your ankle joint. We have designed a new way of looking for these things which consists of clinical tests and surveys. We would like you to do the assessment to assist us understanding this.

4 Why have I been asked?

You have been asked to join in this study because you have bled into your ankle joints before, but in your daily life it doesn't really bother you. You will not be able to take part if you have had any major surgery or procedures on your ankle, if you have regular bleeds into any other lower limb joint, and finally if you have any other condition that might affect your balance. Finally, if a member of the Haemophilia Centre staff has told you that your ankle joint has arthritis, then you cannot take part. Also, if you decide to take part and you have an ankle or knee bleed within 6 weeks of the appointment date or on the day itself, then we will change it.

5 Do I have to take part?

It is totally up to you to decide. We will describe the study and go through this information sheet, which you can then take away. Please use it to help you decide whether you want to take part. If you decide that you would like to take part, then as you are less than 18 years of age, please ask a parent or guardian to sign the attached Consent Forms and return one to us in the envelope provided. We would also like you to sign the consent form so that we know that you have fully understood the study. Keep a copies for yourself. You are free to stop being in the study at any point without telling us why. You will not be affected in any way by deciding to not take part or stop.

6 What will happen to me if I take part?

You will be asked to come to a treatment centre for one visit. You will be asked to write the answers some questions, a lot are tick boxes, and also to do some simple clinical tests. An ankle assessment that you have already experienced as part of your normal care will be repeated followed by a set of clinical tests used to measure parts of your strength, flexibility, balance and fitness. Depending on how your condition shows itself, you may or may not have done these tests before. For one test, we will video you performing a movement for analysis after the session; these images will be deleted after grading. The questionnaires will be alternated with the clinical tests to allow you to rest in between. The questions will also be about flexibility and exercise. We expect that this whole process will take no longer than 1.45 hours in total. Depending on your answers to

the exercise questionnaire, we may contact you to do a 30 minute follow up interview to make sure we have learned and understood as much as possible. This interview would be recorded. We would also like to look at your medical records to access data about your haemophilia so that we do not have to use your time to ask you. Please inform us if you do not want us to do this. Also, although the balance tests etc are very gentle and simple we would like to make extra sure that you are not at risk of having a bleed. So please would you use some prophylaxis on the appointment day. We will check your blood pressure and heart rate on the day of testing to make sure you are fit enough to take part.

Please bring shorts and trainers with you.

7 Are there any risks or disadvantages to taking part?

An ankle test will be done that has already been done to you before followed by a set of tests used to measure your flexibility and balance. The prophylaxis that you have used gives some protection against having a bleed. I will ask you before we begin testing to make sure that you have remembered to use it. If you have not, we may do the testing on another day. Please tell me straight away during the testing if you should feel any discomfort or are worried in any way.

8 What are the possible benefits of taking part?

It is not likely that there will be a benefit to you straight away but the information we gain from this study will allow us to improve our understanding of the things that might play a part in why some people bleed into their ankles more than others.

9 What if there is a problem?

*Any complaint about the way you have been dealt with during the study or any possible harm that might have happened can be addressed by contacting my supervisor, Dr Pratima Chowdary. Or you can contact the Patient Advice and Liaison Service (PALS) on * For further contact details see the bottom of the information sheet.*

10 Will my taking part in the study be kept private?

The information you provide during the study and information about your haemophilia will be entered on an electronic spreadsheet. This will be stored on an encrypted NHS computer. You will only be known by a code on the spreadsheet and nothing that can identify you, like your date of birth, will be recorded. Only researchers will be able to access this information. This information will be kept until the series of studies is finished and then it will be destroyed. Copies of consent forms, study record forms and results will be kept in a special study folder. This will be kept in a locked room that is used only for research.

11 What will happen to the results of the research study?

This study is part of a higher degree. The results of all the people taking part in the study will be put into statistical equations to see if we can find any relationships between the things that we tested for and a person's likelihood of bleeding into their ankle. For the questions where you wrote your answers, we will use text exploration to see if we can establish any relationships there.

The results of the study will also be presented at National and International meetings and in scientific journals.

12 Who has reviewed the study?

This study has been reviewed and approved by the Faculty of Health and Social Science Research Ethics and Governance Committee, University of Brighton and the NHS Research Ethics Committee (London - Hampstead Area).

13 Contacts for further information

PhD Principal Investigator

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*Individual centres local office number will be entered here.

E Appendix 18 Case-Control Study: Information Sheet Young Person, Haemophilia Control

**University of Brighton
Centre for Clinical Research**

Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia.

Young Person's Information Sheet

Group 2 Haemophilia with No Joint Problems

1 Study title

Evaluation of the Effect of Musculoskeletal Factors on the Development of Joint Disease in Haemophilia.

2 Invitation

We would like you to help us with some research. It is important that you understand what the research is for and what you would be asked to do. Please take time to read this information sheet carefully. Ask us if anything is not clear. Also ask if you would like more information. Take time to decide if you would like to take part.

3 What is the reason for the study?

In this study we are hoping to find out whether things other than haemophilia affect how much or how often someone bleeds into their ankle joint. We have designed a new way of looking for these things which consists of clinical tests and surveys. We would like you to do the assessment to assist us in understanding this.

4 Why have I been asked?

You have been invited to take part in this study because you have haemophilia with no history of joint problems. Unfortunately you will not be able to take part if you have had any major surgery or procedures on your ankles or knees or if you have any condition that might affect your balance. Finally, if a member of the Haemophilia Centre staff has told you that your ankle joint has arthritis, then you cannot take part. Also, if you decide to take part and you have an ankle or knee bleed within 6 weeks of the appointment date or on the day itself, then we will change it.

5 Do I have to take part?

It is totally up to you to decide. We will describe the study and go through this information sheet, which you can then take away. Please use it to help you decide whether you want to take part. If you decide that you would like to take part, then as you are less than 18 years of age, please ask a parent or guardian to sign the attached Consent Forms and return one to us in the envelope provided. We would also like you to sign the consent form so that we know that you have fully understood the study. Keep copies of both forms for yourself. You are free to stop being in the study at any point without telling us why. You will not be affected in any way by deciding to not take part or stop.

6 What will happen to me if I take part?

You will be asked to come to a treatment centre for one visit. You will be asked to write the answers some questions, a lot are tick boxes, and also to do some simple clinical tests. An ankle assessment that you have already experienced as part of your normal care will be repeated followed by a set of clinical tests used to measure parts of your strength, flexibility, balance and fitness. Depending on how your condition shows itself, you may or may not have done these tests before. For one test, we will video you performing a movement for analysis after the session; these images will be deleted after grading. The questionnaires will be alternated with the clinical tests to allow you to rest in between. The questions will also be about flexibility and exercise. We expect that this whole process will take no longer than 1.45 hours in total. Depending on your answers to the exercise questionnaire, we may contact you to do a 30 minute follow up interview to make sure we have learned and understood as much as possible. This interview would be recorded. We would

also like to look at your medical records to access data about your haemophilia so that we do not have to use your time to ask you. Please inform us if you do not want us to do this. Although the balance tests etc are very gentle and simple we would like to make extra sure that you are not at risk of having a bleed. So if you normally use prophylaxis before exercise please make sure that you have used some before taking part. We will check your blood pressure and heart rate on the day of testing to make sure you are fit enough to take part.

Please bring shorts and trainers with you.

7 Are there any risks or disadvantages to taking part?

Prophylaxis gives some protection against having a bleed. I will ask you before we begin testing to make sure that you have remembered to use it. If you normally would have but have forgotten, we may do the testing on another day. Please tell me straight away during the testing if you should feel any discomfort or are worried in any way.

8 What are the possible benefits of taking part?

It is not likely that there will be a benefit to you straight away but the information we gain from this study will allow us to improve our understanding of the things that might play a part in why some people bleed into their ankles more than others.

9 What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm that might have happened can be addressed by contacting my supervisor, Dr Pratima Chowdary. Or you can contact the Patient Advice and Liaison Service (PALS) on*
For further contact details see the bottom of the information sheet.

10 Will my taking part in the study be kept private?

The information you provide during the study and information about your haemophilia will be entered on an electronic spreadsheet. This will be stored on an encrypted NHS computer. You will only be known by a code on the spreadsheet and nothing that can identify you, like your date of birth, will be recorded. Only researchers will be able to access this information. This information will be kept until the series of studies is finished and then it will be destroyed. Copies of consent forms, study record forms and results will be kept in a special study folder. This will be kept in a locked room that is used only for research.

11 What will happen to the results of the research study?

This study is part of a higher degree. The results of all the people taking part in the study will be put into statistical equations to see if we can find any relationships between the things that we tested for and a person's likelihood of bleeding into their ankle. For the questions where you wrote your answers, we will use text exploration to see if we can establish any relationships there. As part of the study write-up anonymised direct quotes may be used. The results of the study will also be presented at National and International meetings and in scientific journals.

12 Who has reviewed the study?

This study has been reviewed and approved by the Faculty of Health and Social Science Research Ethics and Governance Committee, University of Brighton and the NHS Research Ethics Committee (London - Hampstead Area).

13 Contacts for further information

PhD Principal Investigator

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*Individual centres local office number will be entered here.

E Appendix 19 Case-Control Study: Information Sheet Young Person, Normal Volunteer

**University of Brighton
Centre for Clinical Research**

Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia. Young Person's Information Sheet Group 4 Healthy Ankles

1 Study title

Evaluation of the Effect of Musculoskeletal Factors on the Development of Joint Disease in Haemophilia

2 Invitation

We would like you to assist us with some research. It is important that you understand what the research is for and what you would be asked to do. Please take time to read this information sheet carefully. Ask us if anything is not clear. Also ask if you would like more information. Take time to decide if you would like to take part.

3 What is the reason for the study?

In this study we are hoping to find out whether things other than haemophilia (pronounced heem-o-feel-ee-a) affect how much or how often someone with moderate or severe haemophilia bleeds into their ankle joint. Haemophilia is a condition that some boys and men are born with. Sometimes they bleed into their joints and in particular the ankle. This eventually causes damage that we can't reverse. We cannot cure haemophilia yet and so we are trying to find other ways of preventing the joint damage. In order to do this we need to compare people with and without haemophilia and with and without joint ankle joint problems. We believe that certain clinical tests and surveys might give us clues to figuring this out. No injections or blood tests are involved. We would like you to do the assessment to assist us in understanding this condition.

4 Why have I been asked?

You have been invited to take part in this study because you have never had a history of problems with your ankle joints. Unfortunately you will not be able to take part if you have had any major surgery or procedures on your ankles or knees, or if you have any condition that might affect your balance. Also, if you decide to take part, your visit may be delayed if you have a new injury to your ankle within 6 weeks of the visit date or if one is present on day of testing.

5 Do I have to take part?

It is totally up to you to decide. We will describe the study and go through this information sheet, which you can then take away. Please use it to help you decide whether you want to take part. If you decide that you would like to take part, then as you are less than 18 years of age, please ask a parent or guardian to sign the attached Consent Forms and return one to us in the envelope provided. We would also like you to sign the consent form so that we know that you have fully understood the study. Keep copies of both forms for yourself. You are free to stop being in the study at any point without telling us why. You will not be affected in any way by deciding to not take part or stop.

6 What will happen to me if I take part?

You will be asked to come to a treatment centre for one visit. You will be asked to write the answers some questions, a lot are tick boxes, and also to do some simple clinical tests. The set of clinical tests are used to measure parts of your strength, flexibility, balance and fitness. For one test, we will video you performing a movement for analysis after the session; these images will be deleted after grading. The surveys will be alternated with the clinical tests to allow you to rest in between. The questions will also be about flexibility and exercise. We expect that this whole process will take no longer than 1.45 hours in total.

We will check your blood pressure and heart rate on the day of testing to make sure you are fit enough to take part.

Please bring shorts and trainers with you.

7 Are there any risks or disadvantages to taking part?

The tests that you will be performing are considered to be low risk but please tell me straight away during the testing if you should feel any discomfort or are worried in any way.

8 What are the possible benefits of taking part?

There is no immediate benefit to you in taking part in this research, but the information will allow us to improve our understanding of the things that contribute to the development of ankle joint disease in people with haemophilia.

9 What if there is a problem?

*Any complaint about the way you have been dealt with during the study or any possible harm that might have happened can be addressed by contacting my supervisor, Dr Pratima Chowdary. Or you can contact the Patient Advice and Liaison Service (PALS) on * For further contact details see the bottom of the information sheet.*

10 Will my taking part in the study be kept private?

The information you provide during the study and information about your haemophilia will be entered on an electronic spreadsheet. This will be stored on an encrypted NHS computer. You will only be known by a code on the spreadsheet and nothing that can identify you, like your date of birth, will be recorded. Only researchers will be able to access this information. This information will be kept until the series of studies is finished and then it will be destroyed.

Copies of consent forms, study record forms and results will be kept in a special study folder. This will be kept in a locked room that is used only for research.

11 What will happen to the results of the research study?

This study is for a higher degree. The results of all the people taking part in the study will be put into statistical equations to see if we can find any relationships between the things that we tested for and a person's likelihood of bleeding into their ankle. For the questions where you wrote your answers, we will use text exploration to see if we can establish any relationships there. As part of the study write-up anonymised direct quotes may be used.

The results of the study will also be presented at National and International meetings and in scientific journals.

12 Who has reviewed the study?

This study has been reviewed and approved by the Faculty of Health and Social Science Research Ethics and Governance Committee, University of Brighton and the NHS Research Ethics Committee (London - Hampstead Area).

13 Contacts for further information

PhD Principal Investigator

Co-Principal Investigator (Clinical Supervisor)

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*Individual centres local office number will be entered here.

E Appendix 20 Case-Control Study: Information Sheet, Parent, Haemophilia Ankle

**University of Brighton
Centre for Clinical Research**

Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia.

Information Sheet for Parents

Group 1 Haemophilia with Ankle Problems

1 Study title

Evaluation of the Effect of Musculoskeletal Factors on the Development of Joint Disease in Haemophilia

2 Invitation

Your child has been invited to take part in a research study. Before you decide whether they can take part, you need to understand why the research is being done and what it would involve for your child. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish them to take part.

3 What is the purpose of the study?

In this study we are hoping to find out whether things other than the haemophilia itself affect how much or how often your child bleeds into their ankle joint. We have developed a new assessment tool to help us determine this which consists of clinical tests and surveys. No blood tests or injections are involved. We are asking your child to undergo the assessment in order to help us understand this condition.

4 Why has my child been invited?

Your child has been invited to take part in this study because they have a history of bleeding their ankle joints but currently it is not troubling them greatly in their day to day activities. Unfortunately they will not be able to take part if they have had any major surgery or procedures on their ankle, if any of their other lower limb joints are badly affected by joint disease, and finally if they have any other condition that might affect their balance. Also, if they decide to take part, their visit may be postponed if they have experienced an ankle or knee bleed within 6 weeks of the visit date or if one is present on day of testing.

5 Do they have to take part?

It is up to you to decide; it is totally voluntary. We will describe the study and go through this information sheet, which we will then give to you. Please take it away and decide whether you would like your child to help us in this research. If you decide that they can take part, then please read and sign the attached Consent Forms and return one to us in the envelope provided, keeping a copy for your own records. Your child is free to withdraw at any time, without giving a reason. They will not be affected in any way by a decision not to take part or withdraw.

6 What will happen to my child if they take part?

They will be asked to attend a treatment centre on one occasion. They will be asked to answer some questions and also to perform some simple clinical tests. An ankle assessment that they have already experienced as part of normal care will be repeated followed by a set of clinical tests used to measure aspects of strength, flexibility, balance and fitness. Depending on how your child's condition shows itself, they may or may not have done these tests before. For one test, we will video your child performing a movement for analysis after the session; these images will be deleted after grading. The questionnaires will be alternated with the clinical tests to allow them to rest in between. The questions

will also be about flexibility and exercise. We expect that this whole process will take no longer than 1.45 hours in total. Depending on their answers to the exercise questionnaire, we may contact you to do a 30 minute follow up interview to make sure we have learned and understood as much as possible. This interview would be recorded. We would also like to look at their medical records to access data about their haemophilia so that we do not have to use your time to ask you. Please inform us if you do not want us to do this.

Also, whilst we are confident that the clinical tests being used are low risk, we would ask that you ensure that your child has used some prophylaxis in order to be doubly sure.

Please bring shorts and trainers with you.

7 What are the possible disadvantages and risks of taking part?

The prophylaxis that your child has taken offers some protection against sustaining a bleed. I will ask whether prophylaxis has been used before we begin. If it has not, we may consider re-arranging the appointment. I would encourage you to remind your child to please inform me immediately during the testing if they should feel any discomfort or are concerned in any way.

8 What are the possible benefits of taking part?

There may not be an immediate benefit to your child in taking part in this research, but the information will allow us to improve our understanding of the things that contribute to the development of ankle joint disease in people with haemophilia.

9 What if there is a problem?

*Any complaint about the way you or your child have been dealt with during the study or any possible harm your child might have suffered can be addressed by contacting my supervisor, Dr Pratima Chowdary. Alternatively you can contact the Patient Liaison and Advice Service (PALS) on * For further contact details see the bottom of the information sheet*

10 Will my child's taking part in the study be kept confidential?

The information your child provides during the assessment and information about their haemophilia will be entered on an electronic spreadsheet which will be stored on an encrypted NHS computer. Your child will be referred to by a reference code on the spreadsheet and no personal identifiable information will be stored. Only the researchers will be able to access this information. This information will be kept until the series of studies is completed when it will be destroyed, approximately 3 years. Copies of consent forms, case record forms, and results will be filed in a dedicated study folder and stored in a locked room dedicated for clinical trials and studies.

11 What will happen to the results of the research study?

This study is part of a PhD programme. The results of all the people taking part in the study will be analysed both by statistics and text exploration to see if we can establish any relationships between the things that we tested for and a person with haemophilia's tendency to develop ankle joint disease. As part of the study write-up anonymised direct quotes may be used. The results of this study will also be presented at National and International meetings and in peer-reviewed journals.

12 Who has reviewed the study?

This study has been reviewed and approved by the Faculty of Health and Social Science Research Ethics and Governance Committee, University of Brighton and the NHS Research Ethics Committee (London - Hampstead Area).

13 Contacts for further information

PhD Principal Investigator

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*Individual centres local office number to be entered here.

E Appendix 21 Case-Control Study: Information Sheet, Parent, Haemophilia Control

**University of Brighton
Centre for Clinical Research**

**Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia. Information Sheet for Parents Group 2 Haemophilia
with No Joint Problems**

1 Study title

Evaluation of the Effect of Musculoskeletal Factors on the Development of Joint Disease in Haemophilia.

2 Invitation

Your child has been invited to take part in a research study. Before you decide whether they can take part, you need to understand why the research is being done and what it would involve for your child. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish them to take part.

3 What is the purpose of the study?

In this study we are hoping to find out whether things other than the presence of haemophilia, affect how much or how often a person with moderate or severe haemophilia bleeds into their ankle joint. People with moderate and severe haemophilia sometimes bleed into their joints and in particular the ankle. This eventually causes irreversible damage. As we cannot cure haemophilia, we are trying to find other ways of preventing joint damage. In order to do this, we need to compare people with and without haemophilia who do and do not have a problem with their ankle joint(s). We have developed a new assessment tool to help us determine this which consists of clinical tests and surveys. No blood tests or injections are involved. We are asking your child to undergo the assessment to help us understand this condition.

4 Why has my child been invited?

Your child has been invited to take part in this study because they have haemophilia with no history of bleeding into their ankle joints. Unfortunately they will not be able to take part if they have had any surgery or procedures on their ankle, if any of their other lower limb joints are affected by regular bleeds, or if they have any condition that might affect their balance. Also, should you decide that they can take part, their visit may be postponed if they have experienced an ankle or knee bleed within 6 weeks of the visit date or if one is present on day of testing.

5 Do they have to take part?

It is up to you to decide; it is totally voluntary. We will describe the study and go through this information sheet, which we will then give to you. Please take it away and decide whether you would like your child to help us in this research. If you decide that they can take part, then please read and sign the attached Consent Forms and return one to us in the envelope provided, keeping a copy for your own records. Your child is free to withdraw at any time, without giving a reason. They will not be affected in any way by a decision not to take part or withdraw.

6 What will happen to my child if they take part?

You will be asked to attend a treatment centre on one occasion. They will be asked to answer some questions and also to perform some simple clinical tests. An ankle assessment that they have already experienced as part of normal care will be repeated followed by a set of clinical tests used to measure aspects of strength, flexibility, balance and fitness. Depending on your child's condition, they may or may not have done these tests before. For one test, we will video your child performing a movement for analysis after the session; these images will be deleted after grading. The questionnaires will be alternated with the clinical tests to allow them to rest in between. The

questions will also be about flexibility and exercise. We expect that this whole process will take no longer than 1.45 hours in total. Depending on their answers to the exercise questionnaire, we may contact you to do a 30 minute follow up interview to make sure we have learned and understood as much as possible. This interview would be recorded. We would also like to look at their medical records to access data about their haemophilia only so that we do not have to use your time to ask you. Please inform us if you do not want us to do this.

Also, whilst we are confident that the clinical tests being used are low risk, we would ask that if you normally use prophylaxis before exercise that you ensure that you have used some before taking part. We will check your blood pressure and heart rate on the day of testing to make sure you are fit enough to take part.

Please bring shorts and trainers with you.

7 What are the possible disadvantages and risks of taking part?

If your child has used prophylaxis it will offer some protection against sustaining a bleed. I will ask whether they have used prophylaxis before we begin. If they have not and they normally would, we may consider re-arranging the appointment. I would encourage you to remind your child to please inform me immediately during the testing if they should feel any discomfort or are concerned in any way.

8 What are the possible benefits of taking part?

There may not be an immediate benefit to your child in taking part in this research, but the information will allow us to improve our understanding of the things that contribute to the development of ankle joint disease in people with haemophilia.

9 What if there is a problem?

Any complaint about the way you or your child have been dealt with during the study or any possible harm your child might have suffered can be addressed by contacting, Dr Pratima Chowdary. Alternatively you can contact the Patient Liaison and Advice Service (PALS) on

*.....**
For further contact details see the bottom of the information sheet

10 Will my child's taking part in the study be kept confidential?

The information your child provides during the assessment and information about their haemophilia will be entered on an electronic spreadsheet which will be stored on an encrypted NHS computer. Your child will be referred to by a reference code on the spreadsheet and no personal identifiable information will be stored. Only the researchers will be able to access this information. This information will be kept until the series of studies is completed when it will be destroyed, approximately 3 years.

Copies of consent forms, case record forms, and results will be filed in a dedicated study folder and stored in a locked room dedicated for clinical trials and studies.

11 What will happen to the results of the research study?

This study is part of a PhD programme. The results of all the people taking part in the study will be analysed both by statistics and exploration of written answers to see if we can establish any relationships between the things that we tested for and a person with haemophilia's tendency to develop ankle joint disease. As part of the study write-up anonymised direct quotes may be used. The results of this study will also be presented at National and International meetings and in peer-reviewed journals.

12 Who has reviewed the study?

This study has been reviewed and approved by the Faculty of Health and Social Science Research Ethics and Governance Committee, University of Brighton and the NHS Research Ethics Committee (London – Hampstead Area).

13 Contacts for further information

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Co-Principal Investigator (Clinical Supervisor)

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E Appendix 22 Case-Control Study: Information Sheet, Parent, Normal Volunteer

**University of Brighton
Centre for Clinical Research**

Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia. Information Sheet for Parents **Group 4 Healthy Ankles**

1 Study title

Evaluation of the Effect of Musculoskeletal Factors on the Development of Joint Disease in Haemophilia

2 Invitation

Your child has been invited to take part in a research study. Before you decide whether they can take part, you need to understand why the research is being done and what it would involve for your child. Please take time to read the following information carefully. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish them to take part.

3 What is the purpose of the study?

In this study we are hoping to find out whether things other than the presence of haemophilia, affect how much or how often a person with moderate or severe haemophilia bleeds into their ankle joint. Haemophilia (pronounced heem-o-feel-ee-a) is an inherited bleeding disorder affecting boys and men. Bleeds occur into their joints and in particular the ankle. This eventually causes irreversible damage. As we cannot cure haemophilia, we are trying to find other ways of preventing joint damage. In order to do this, we need to compare people with and without haemophilia who do and do not have a problem with their ankle joint(s). We have developed a new assessment tool to help us determine this which consists of clinical tests and surveys. No blood tests or injections are involved. We are asking your child to undergo the assessment to help us understand this condition.

4 Why has my child been invited?

Your child has been invited to take part in this study because they have no history of ankle joint problems. Unfortunately they will not be able to take part if they have had any major surgery or procedures on their ankles or knees, or if they have any condition that might affect their balance. Also, should they decide to take part, their visit will be cancelled if they experience a new injury to their ankle as they will no longer be eligible.

5 Do they have to take part?

It is up to you to decide; it is totally voluntary. We will describe the study and go through this information sheet, which we will then give to you. Please take it away and decide whether you would like your child to help us in this research. If you decide that they can take part, then please read and sign the attached Consent Forms and return one to us in the envelope provided, keeping a copy for your own records. Your child is free to withdraw at any time, without giving a reason. They will not be affected in any way by a decision not to take part or withdraw.

6 What will happen to my child if they take part?

You will be asked to attend the Haemophilia Centre on one occasion. They will be asked to answer some questions and also to perform some simple clinical tests. The clinical tests will be used to measure aspects of strength, flexibility, balance and fitness. For one test, we will video your child performing a movement for analysis after the session; these images will be deleted immediately after grading. The questionnaires will be alternated with the clinical tests to allow rest in between. The questions will also be about flexibility and exercise. We expect that this whole process will take no longer than 1.45 hours in total. We will check their blood pressure and heart rate on the day of testing to make sure they are fit enough to take part.

Please bring shorts and trainers with you.

7 What are the possible disadvantages and risks of taking part?

The tests that they will be performing are considered to be low risk but I would encourage you to remind your child to please inform me immediately during the testing if they should feel any discomfort or are concerned in any way.

8 What are the possible benefits of taking part?

There is not an immediate benefit to your child in taking part in this research but the information will allow us to improve our understanding of the things that contribute to the development of ankle joint disease in people with haemophilia.

9 What if there is a problem?

Any complaint about the way you or your child have been dealt with during the study or any possible harm your child might have suffered can be addressed by contacting my supervisor, Dr Pratima Chowdary. Alternatively you can contact the Patient Liaison and Advice Service (PALS) on For further contact details see the bottom of the information sheet*

10 Will my child's taking part in the study be kept confidential?

The information your child provides during the assessment and information about their haemophilia will be entered on an electronic spreadsheet which will be stored on an encrypted NHS computer. Your child will be referred to by a reference code on the spreadsheet and no personal identifiable information will be stored. Only the researchers will be able to access this information. This information will be kept until the series of studies is completed when it will be destroyed, approximately 3 years.

Copies of consent forms, case record forms, and results will be filed in a dedicated study folder and stored in a locked room dedicated for clinical trials and studies.

11 What will happen to the results of the research study?

This study is part of a PhD programme. The results of all the people taking part in the study will be analysed both by statistics and text exploration to see if we can establish any relationships between the things that we tested for and a person with haemophilia's tendency to develop ankle joint disease. As part of the study write-up anonymised direct quotes may be used. The results of this study will also be presented at National and International meetings and in peer-reviewed journals.

12 Who has reviewed the study?

This study has been reviewed and approved by the Faculty of Health and Social Science Research Ethics and Governance Committee, University of Brighton and the NHS Research Ethics Committee (London-Hampstead Area).

13 Contacts for further information

PhD Principal Investigator

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p.chowdary@nhs.net

*Individual centres local office number to be entered here.

E Appendix 23 Case Control Study: Consent Form Young Person, Haemophilia Groups

University of Brighton, Centre for Clinical Research

Consent Form, age 12 – 17 years

Title of Project: Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia.

Name: _____ MRN No.: _____

Date of birth: _____

You are asked to please circle all the statements that you agree with:

I have read about this study YES / NO

Someone else has also explained about this study YES / NO

I understand what this study is about YES / NO

I have asked all the questions that I want to YES / NO

My questions have been answered so that I understand clearly YES / NO

I understand that it is ok to stop taking part at any time YES / NO

I understand that my medical notes will be looked at as part of the study YES / NO

I understand that for one of the tests I will be video'd so that the researcher can check the images later, it will then be deleted YES / NO

I am happy to take part YES / NO

If any of the answers is "NO" or if you **don't** want to take part, **don't** sign your name!

If you do want to take part, please sign your name and put today's date, thank you.

Statement of consent:

I understand that my parent(s) or legally authorised representatives (if applicable) have given permission for me to take part in this study. They and/or a member of my healthcare team have explained the study to me and have answered my questions. I voluntarily agree to be in this study.

.....
Name of young person, Date & Signature,

.....
Name of person obtaining consent, Date & Signature

Upon signing, the parent or legal guardian will retain a copy of this form, and another will be held in the participant's research record.

E Appendix 24 Case Control Study: Consent Form Parent, Haemophilia Groups

University of Brighton
Centre for Clinical Research

Parental Consent Form

Title of Project: Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia.

Name: _____

MRN No.: _____

Date of birth: _____

Name of Researcher: Ann McCarthy

Initials

1. I confirm that I have read and understand the information sheet which included a statement concerning the purpose, methods, demands, possible risks and inconveniences of this study dated I have had the opportunity to consider the information and ask questions, which have been answered to my satisfaction.
2. I will remind my child to inform the principal investigator if they have any symptoms of pain or discomfort during or after the clinical tests.
3. I understand that my child's participation is voluntary and that they are free to withdraw at any time without giving any reason.
4. I have the right to ask to see the data collected about my child and if anything is incorrect, I can ask for it to be corrected.
5. I understand that my child's medical records will be reviewed for data specific to this study only.
6. I understand that one test will involve a video recording which will be erased immediately after grading by the investigator.
7. As parent or legal guardian, I authorise _____ (child's name) to become a participant in the research study as described in the information sheet.

.....
Name of parent or legal guardian, Date & Signature,

.....
Name of Researcher, Date & Signature

Upon signing, the parent or legal guardian will retain a copy of this form, and another will be held in the participant's research record.

E Appendix 25 Case Control Study: Consent Form Adult, Normal Volunteers

University of Brighton
Centre for Clinical Research

Participant Consent Form

Title of Project: Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia.

Name: _____
 Initials

MRN No.: _____

Date of birth: _____

Name of Researcher: Ann McCarthy

1. I confirm that I have read and understand the information sheet that included a statement concerning the purpose, methods, demands, possible risks and inconveniences of this study dated I have had the opportunity to consider the information and ask questions, which have been answered to my satisfaction.
2. I will inform the principal investigator if I have any symptoms of pain or discomfort during or after the clinical tests.
3. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.
4. I have the right to ask to see the data collected about me and if anything is incorrect, I can ask for it to be corrected.
5. I understand that my medical records will be reviewed for data specific to this study only.
6. I understand that one test will involve a video recording which will be erased immediately after grading by the investigator.
7. I agree to take part in the above study.

.....
Name of Participant, Date, Signature

.....
Name of Researcher, Date, Signature

Upon signing, the participant will retain a copy of this form, and the another will be held in the participant's research record.

E Appendix 25 Case Control Study: Consent Form Young Person, Normal Volunteers

Consent Form, age 12 – 17 years

Title of Project: Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia.

Name: _____ MRN No.: _____

Date of birth: _____

You are asked to please circle all the statements that you agree with:

I have read about this study YES / NO

Someone else has also explained about this study YES / NO

I understand what this study is about YES / NO

I have asked all the questions that I want to YES / NO

My questions have been answered so that I understand clearly YES / NO

I understand that it is ok to stop taking part at any time YES / NO

I understand that my medical notes will be looked at as part of the study YES / NO

I understand that for one of the tests I will be video'd so that the researcher can check the images later, it will then be deleted YES / NO

I am happy to take part YES / NO

If any of the answers is "NO" or if you **don't** want to take part, **don't** sign your name!

If you do want to take part, please sign your name and put today's date, thank you.

Statement of consent:

I understand that my parent(s) or legally authorised representatives (if applicable) have given permission for me to take part in this study. They and/or a member of my healthcare team have explained the study to me and have answered my questions. I voluntarily agree to be in this study.

.....
Name of young person, Date & Signature,

.....
Name of person obtaining consent, Date & Signature

Upon signing, the parent or legal guardian will retain a copy of this form, and another will be held in the participant's research record.

E Appendix 26 Case Control Study: Consent Form Parent, Normal Volunteers

Parental Consent Form

Title of Project: Evaluating how joint, muscular and exercise factors affect the development of joint disease in haemophilia.

Name: _____

MRN No.: _____

Date of birth: _____

Name of Researcher: Ann McCarthy

Initials

1. I confirm that I have read and understand the information sheet which included a statement concerning the purpose, methods, demands, possible risks and inconveniences of this study dated I have had the opportunity to consider the information and ask questions, which have been answered to my satisfaction.
2. I will remind my child to inform the principal investigator if they have any symptoms of pain or discomfort during or after the clinical tests.
3. I understand that my child's participation is voluntary and that they are free to withdraw at any time without giving any reason.
4. I have the right to ask to see the data collected about my child and if anything is incorrect, I can ask for it to be corrected.
5. I understand that my child's medical records will be reviewed for data specific to this study only.
6. I understand that one test will involve a video recording which will be erased immediately after grading by the investigator.
7. As parent or legal guardian, I authorise _____ (child's name) to become a participant in the research study as described in the information sheet.

.....
Name of parent or legal guardian, Date & Signature,

.....
Name of Researcher, Date & Signature

Upon signing, the parent or legal guardian will retain a copy of this form, and another will be held in the participant's research record.

**EVALUATION OF MUSCULOSKELETAL & EXERCISE FACTORS
ON THE DEVELOPMENT OF JOINT DISEASE IN HAEMOPHILIA.**

STANDARD OPERATING PROCEDURES FOR DATA COLLECTION

AUTHOR: ANN MCCARTHY

VERSION: 0.03

DATE: 18/11/2014

INTRODUCTION

- The purpose of this document is to ensure that all data collection occurs in a uniform manner and that recording is standardised.
- This is not the case record form but rather an explanatory guide.
- Each test and survey used during this study is described in detail in terms of its purpose, procedure and recording.
- As this is a between groups correlational study, not all data collection applies to each group. Therefore, at the top of each new test the applicable groups are indicated. The groups are as follows:
 1. Moderate or severe haemophilia with established clinically mild ankle arthropathy
 2. Haemophilia with no established joint disease
 3. Non-haemophilia chronic ankle instability
 4. Healthy controls
- Tests are presented in the order in which they will be performed.
- Where tests are available with visual guides from originating authors or similar, these will also be provided, e.g. the Foot Posture Index
- Facilities – space is needed in order to lay out a template for performing the Star Excursion Balance Test (SEBT) of about 2m². Also, clear wall space in order to perform the ankle lunge test where at the base of the wall, the floor is met with a clear 90° angle so as to allow for accurate distance measuring. Additional equipment to be supplied by each centre: plinth; a standard chair; blood pressure monitor and weighing scales; either desk space or clipboard to facilitate the completion of questionnaires; pens; tape to fix the SEBT template to the floor – masking, zinc oxide strapping or mepore should leave no residue. Finally refreshments (water or squash etc) for the participant. All other equipment will be provided by the co-ordinating centre.
- The investigator additionally requires a coin, smart phone with the **Slick Metronome** downloaded or music may be provided to facilitate the step test (see instructions).
- Please complete the surveys with a black pen to aid scanning. Please ask participants to tick clearly within the boxes or to write numbers clearly.
- In the CRF, hashed boxes are for completion after the participant has left.

ON THE DAY PREPARATIONS

- Affix the SEBT template to the floor using tape. Start with a perpendicular line, taping at each end. Work to the corners on one side. Then the other perpendicular and corners. It doesn't have to be perfectly wrinkle free, but make sure the participant won't be able to take up slack when touching down. The laser measure will cope with any wrinkles present.
- Put down two pieces of zinc oxide approximately 25cm long perpendicular to the wall. Mark them as left and right. Make sure the chosen wall drops to a clear angle at the junction with the floor or this may affect measured distances. Doors and door frames are good for this – bear health and safety issues in mind.
- Place the exercise step with a chair next to it for the step test.
- Figure out where you are going to balance your smart phone camera (tripod provided) to capture full body images. Approximately a 2.75m distance is needed.
- Arrange your questionnaires in the order that they will be used.
- Group the marker pencil, goniometer, cloth tape and strapping tape by the plinth.

SCREENING CRITERIA

GROUPS 1 & 2

Medical Records Data Set

It is acknowledged that not all data will be available at each site. Therefore please complete as able.

GROUP 1 & 3

Please screen the above groups using the chronic ankle instability screening tool. As this will allow us to sub-categorise them according to the latest definitions using recurrent sprain, perceived instability and mechanical instability (following anterior drawer test).

For Group 3 participants who present with other complaints, these should be noted along with time since diagnosis.

STUDY PROCEDURES

Name	Physical Activity Questionnaire
Groups	All – ensure correct questionnaire used. There are versions depending on haemophilia or non-haemophilia. Also there are adult and young person versions with appropriate language alterations.
Purpose	It is intended to gather information regarding historical activity patterns and occupation. Piloted but not validated.
Equipment	Questionnaire & pen.
Procedure	As this is an exploratory item, it has been decided that the researcher may assist the participant if they require clarity on any of the questions. Questions may be read out. Some of the questions are structured as visual analogue scales with which participants may be unfamiliar and so the researcher will demonstrate how to complete an example scale and encourage the participant to do another before beginning the questionnaire. Please encourage participant to list all activities including those they may think of as games like climbing trees.
Time	20 minutes.
Recording	Not applicable.

Name	Body Mass Index
Groups	All
Purpose	This measure gives an indication of the percentage body fat of an individual
Equipment	Calibrated weighing scales. Wall, pencil, laser measure or commercial measuring unit. If participant is having assessment during a scheduled clinic visit, nursing colleagues may take these measures as standard.
Procedure	For free measurement of height, the person should be measured bare foot. The individual's hair should be temporarily "flattened" to ensure that the measuring instrument makes contact with the skull. Ensure that the person is looking straight ahead. Legs are straight. Try to ensure that the head, shoulders, buttocks and heels are touching the wall. - Not all may do so, depending on body structure. Use your set square to mark the level and place a small mark and/or a "Post-It". Then use the laser measure to record the height. This can occur while the participant is completing a questionnaire. Follow the instructions for the specific type of weighing scales present in your centre.
Time	2 mins.
Recording	Weight in kilograms (KG) and height in metres (M)

Name	Leg length
Groups	All
Purpose	These measures are for use in later tests or data analysis. Only the foot length is required during the testing session for the star excursion balance test.
Equipment	Pencil and blank sheet of A4 paper. Plinth or bed. Cloth tape measure.
Procedure	Participant lies on a plinth. The data collector fully passively flexes, internally and externally rotates each hip and pulls the leg down straight so that the foot is in line with the hip and in minimal abduction or adduction. The researcher locates the anterior superior iliac spine and places the cloth tape measure on the most prominent point. The participant is asked to hold the tape in position. The researcher then runs the tape to the medial malleolus and notes the distance at the most distal tip. Measure both legs. The participant is asked to stand on the sheet of A4 paper with one foot. The researcher marks the foot length on the paper. Repeat with the second foot. Use the longest measure. Fold the piece of paper across its long axis ensuring that your marks are visible at the folded edge and then put the 2 end marks together and fold to half the foot length. The researcher then uses this to mark the foot length across the centre of the SEBT grid. See picture below.
Time	4 minute total
Recording	All recordings in centimetres (cm).



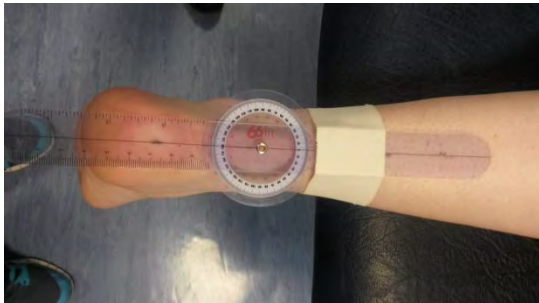
Name	Anterior Drawer Test
Groups	All
Purpose	Assesses the stability of the talocrural joint, in particular the anterior talofibular ligament.
Equipment	Plinth. +/- rolled towel
Procedure	Participant lies or reclines on a plinth. A towel may be placed under the knee for comfort. The researcher stabilises the tibia and fibula anteriorly. The thumb of the tibial hand should palpate just in front of the lateral malleolus over the lateral talar aspect. Using the other hand, the researcher grips around the calcaneus with the foot in around 10° of plantarflexion. The foot is drawn forward and allowed to move into adduction/inversion. The movement is continued until the end-feel is achieved which could be ligamentous (firm), none/soft (ligaments completely insufficient) or hard/stiff (bony or joint restriction). The movement should be applied slowly, at low load and not in a jerky fashion to ensure the end-feel is noted. Test both feet.
Time	1 minute
Recording	Graded 0 – 3. 0 = hypomobile. 1 = normal. 2 = moderately lax but within normal limits (end-feel present). 3 = severely lax.

(Hiller et al 2007; Phisitkul et al 2009)

Name	Great toe extension range
Groups	All
Purpose	To assess the range of extension at the great toe that has been linked with gait abnormalities and predisposition for developing certain injuries.
Equipment	Goniometer + towel.
Procedure	Participant lies or reclines supine on a plinth. Place a towel or pillow behind the knees to ensure the calf muscle complex is lax and there is no windlass tension. Feet are relaxed. Begin the measure with the great toe in line with the long axis of the foot as per the diagram. The goniometer static arm is placed alongside the metatarsal. The toe is passively extended to end of range which should be a tissue stretch as opposed to a bony block. Repeat 3 times and accept maximum range. Test both feet.
Time	3 minutes total
Recording	Range of movement in degrees.

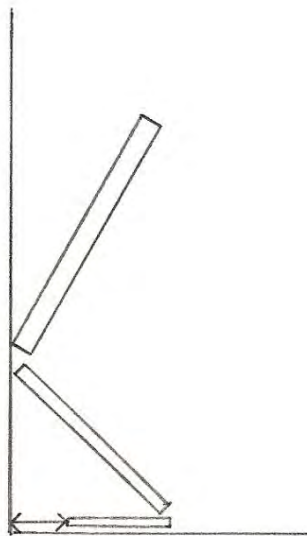


Name	Subtalar inversion and eversion range
Groups	All
Purpose	To assess the range of subtalar inversion and eversion range. This has been linked with gait abnormalities and predisposition for developing several injuries.
Equipment	Goniometer, marker pencil +/- towel.
Procedure	<p>Participant lies prone on a plinth with the foot hanging off the end of the bed. The other leg is placed in a figure four position. A pillow or towel may be placed under the lower leg for patient comfort if necessary. Mark mid calcaneus, a point mid-way between the malleoli and mid-line on the lower calf using the marker pencil. Centre the hinge of the goniometer over the mid-malleolar point. Line up the static arm on the calf and fix down with a piece of strapping tape. The researcher uses their inner thigh to apply a dorsiflexion to gentle resistance or plantigrade. Grasp the calcaneus using the thumb and index, fixing the goniometer moving arm in place. Move the heel from resting to maximal eversion and the range measured. Apply a reasonable amount of pressure to ensure end range is reached. Repeat 3 times and record the greatest measure.</p> <p>The same procedure is followed with inversion.</p> <p>Test both feet. Approximately 9° eversion and 30° inversion (but a wide range of the latter) are average.</p>
Time	5 minutes total
Recording	Range of movement in degrees.

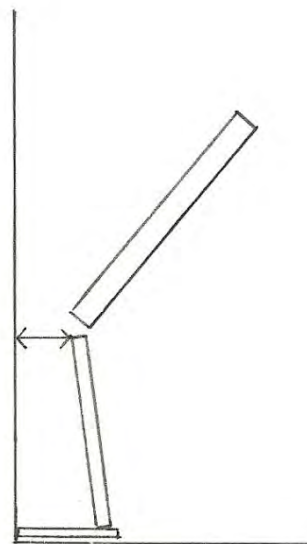


Name	Ankle Lunge Test (ALT)
Groups	All
Purpose	Weight-bearing active measure of ankle joint complex dorsiflexion (the motion is not limited purely to the talocrural joint). There will be some subtalar joint involvement +/- midtarsal motion if the foot moves into pronation through range.
Equipment	Laser measure. Zinc Oxide Tape. Set square. Marker/pencil
Procedure	Test procedure is demonstrated and described by researcher. Researcher aligns the central heel and longest toe on a strip zinc oxide affixed to the floor which is at right angles to the wall (can check this with your set square). The participant lunges forward to touch their knee to a target piece of tape or line on the wall perpendicular to floor tape. They are free to use the wall for balance and place the untested leg in their preferred position of comfort. The participant is asked to keep backing away from the wall until the maximum position is determined. The researcher palpates the heel for lifting. No attempt is made to limit pronation or supination. The researcher marks the tape at the longest toe at the point where the heel just maintains floor contact. Each leg should be measured 3 times. The researcher then uses the laser measure to record the distance from this point to the wall. Use this point to start with the second leg. If the participant is unable to touch the wall then the distance from central patella to wall is recorded using the set square.
Time	4 minutes
Recording	Maximum distance is recorded in centimetres (cm). If the person is unable to touch the wall then the distance from central patella to wall is recorded as a negative result. Positive measures can be completed while participant completes a questionnaire or after attendance.

(Gatt & Chockalingan 2011)



Positive reading.



Negative reading.

Name	Star Excursion Balance Test (SEBT)
Groups	All
Purpose	Assesses intra and inter subject variability in lower limb dynamic balance, strength and co-ordination.
Equipment	Space (approx. 1.9m ²) to place grid on the floor using tape or similar. Non-permanent marker – lipstick works well and applicator (cotton buds). Laser measure. Target. Cleansing wipes. Coin.
Procedure	<p>(Participant's leg length was measured in supine previously.) Procedure is explained and demonstrated. A coin toss will determine which leg will be tested first.</p> <p>The test will occur barefoot. The participant's foot length (measured previously) will be marked exactly across the centre of the grid on the anterior-posterior line. The marker substance will be applied to the participant's toes. The participant places their foot exactly within the foot length marks. With hands on hips, the participant will reach as far as possible along the given vector and lightly touch the ground without taking any weight on the reach leg, this will mark the distance. The participant returns to the start position without touching down where they may then assume a double stance. There will be 5secs rest between trials and 1mins rest between reach directions. Participants will reach in the following three directions: posterior, posteromedial and anterior. Prior to recorded trials, practice trials will be performed. Practice trials will occur in a clockwise/anticlockwise fashion to limit fatigue effects. Three measured trials will occur in each direction.</p> <p style="text-align: center;">A trial will be considered failed and repeated if:</p> <ol style="list-style-type: none"> 1. Person did not touch down, fully applied weight at full reach or missed the target line by more than 5cm 2. Balance lost at any point (hands removed from hips), 3. Stance foot is lifted or twists out of position <p>To measure the distance. Place the right-angle block on the crosshairs in the centre of the grid. Align the laser measure with the reach mark and measure the distance. See picture below. Measure the first leg's distances and then wipe the grid clean. During measurement the participant should sit and rest. They may remove the marker substance with a cleansing wipe. The reach distance will be normalised for leg length as per calculation below.</p>
Time	10mins
Recording	Normalised maximum excursion distance = distance/leg length X 100. Completed while participant completes a questionnaire or after attendance.

(Gribble et al 2012)



Name	Foot Posture Index (FPI)
Groups	All
Purpose	Clinical tool designed to allow a speedy assessment of foot type in clinic without the necessity of measuring tools. Only one point of physical contact with the participant and otherwise the scale is visual. A manual for users of the test has been issued with clear guidance on scoring and definitions.
Equipment	Scoring sheet.
Procedure	<p>Participant is asked to simply stand in a relaxed position looking straight ahead allowing the examiner access to the front and back of the foot. It may be helpful to ask the person to walk on the spot and then assume a standing position. The investigator should be a floor level to easily assess the feet.</p> <p>The six clinical measures taken are:</p> <ol style="list-style-type: none"> 1. Talar head palpation 2. Supra and infra lateral malleolar curvature 3. Calcaneal frontal plane position (rearfoot varus/valgus positioning) 4. Prominence in the region of the talonavicular joint 5. Congruence of the MLA (height and shape) 6. Abduction/adduction of the forefoot on the rearfoot (too-many-toes)
Time	2 minutes
Recording	Simple addition. Completed while participant completes questionnaire or after attendance.

(Redmond et al 2006)

Name	Timed Single Leg Stance
Groups	All
Purpose	To assess static balance ability. Remember this a test of static balance so any marked loss is considered a failed test.
Equipment	Stop watch. Post-it note, piece of Blu-tack or similar.
Procedure	<p>The position for testing will be demonstrated. This is: to stand barefoot, with the other limb raised so that the raised foot is near but not touching the ankle of their stance limb with arms are placed on the hips. The first limb is decided by a coin toss. Participants are asked to focus on a spot on the wall at eye level marked with Blu-tack or similar. The researcher uses a stopwatch to measure the amount of time the subject is able to stand on one limb. Time commences when the subject lifts the foot off the floor. Time ends when the subject either: (1) uses the arms, (2) uses the raised foot (moves it toward or away from the standing limb or touches the floor), (3) moves the weight-bearing foot to maintain balance (i.e., twists foot on the ground), or (4) a maximum of 60 seconds has elapsed. The procedure will be repeated 3 times and each time is recorded. Alternate tests between legs to avoid fatigue. The test will then be repeated in an eyes closed condition. For this condition, allow the participant to assume the position and start timing at closing the eyes.</p> <p>The rests between trials will be carried out according to participant's reported fatigue.</p>
Time	10 minutes maximum
Recording	Balance in seconds.

ame	Hypermobility and dyspraxia scales.
Groups	All
Purpose	To assess for the presence of hypermobility, joint hypermobility syndrome and dyspraxia
Equipment	Questionnaires and goniometer (or eye ball)
Procedure	<p>The majority of this testing is by written questionnaire. The researcher may assist the participant if they require clarification on any question.</p> <p>The Beighton Scale requires an examination for hypermobility as follows: Knee & elbow hyperextension of greater than 10°; 5th MCP joint extension 90°, ability to touch thumb to wrist and ability to stand, bend forward with straight knees and put hands flat to the floor. The first 4 measures are bilateral. Joints whose range is obviously greater than 10° or 90° can be “eye-balled”.</p>
Time	7 minutes including the Beighton scale
Recording	Beighton scale is scored out of 9. Otherwise responses are tick box on a scannable form.

(Clarke 2012; Grahame 2003; Hakim & Grahame 2003)

Name	Single Leg Squat (SLSq)
Groups	All
Purpose	To identify persons presenting with gluteal muscle deficits in a clinical environment without the use of EMG or other expensive equipment.
Equipment	Step approx. 20cm high. Video recorder to assess performance after trials. Smart phone on a stand can be used.
Procedure	<p>Technique is demonstrated by researcher. Shoes are worn. Participant stands on an approximately 20cm step on one leg, arms folded across chest. They are asked to squat 5 times consecutively in a slow controlled manner keeping the foot in full contact with the step, trying to stay balanced at a rate of 1 squat per 2 seconds. 3 practices squats are allowed. The test is videoed for assessment which can occur either during a survey or after the participant leaves.</p> <p>Using a mini-tripod and smart phone a distance of approximately 2.75m is required to adequately frame the participant with the camera in landscape position. The images should be deleted immediately after grading.</p>
Time	4 minutes
Recordings	Visual holistic assessment of performance (poor, fair or good) as per criteria in Table 1. Completed after attendance.

Clinical Rating Criteria Determined by the Consensus Panel		
	Criterion	To be rated "good"
A	Overall impression across the 5 trials	
	- Ability to maintain balance	Participant does not lose balance
	- Perturbations of person	Movement is performed smoothly
	- Depth of squat	The squat is performed to at least 60° of knee flexion
	- Speed of squat	Squat is performed at approximately 1 per 2 seconds
B	Trunk posture	
	- Trunk/thoracic lateral deviation or shift	No trunk/thoracic lateral deviation or shift
	- Trunk/thoracic rotation	No trunk/thoracic rotation
	- Trunk/thoracic lateral flexion	No trunk/thoracic lateral flexion
	- Trunk/thoracic forward flexion	No trunk/thoracic forward flexion
C	The pelvis "in space"	
	- Pelvic shunt or lateral deviation	No pelvic shunt or lateral deviation
	- Pelvic rotation	No pelvic rotation
	- Pelvic tilt (take note of depth of squat)	No pelvic tilt (take note of depth of squat)
D	Hip joint	
	- Hip adduction	No hip adduction
	- Hip (femoral) internal rotation	No hip (femoral) internal rotation
E	Knee joint	
	- Apparent knee valgus	No apparent knee valgus
	- Knee position relative to foot position	Centre of knee remains over the centre of the foot

(Crossley et al 2011)

Name	Ankle plantar flexion strength and endurance test
Groups	All
Purpose	To detect signs of plantarflexor weakness.
Equipment	None. Wall for balance.
Procedure	Participant stands facing the wall, with fingertips on the wall at approximately mid-chest level for balance. One leg is lifted so that the foot is clear of the floor; this is a self-selected position. The participant is then asked to rise up on to their toes to their maximal range as many times as possible before they are unable to continue. The participant may stop at 20 or when the researcher sees fatigue in the muscle in the form of shaking. They then rest for 2 minutes and repeat the process on the other leg. A coin test will determine which leg goes first.
Time	5 minutes
Recording	Number of calf raises on each leg.

Name	Human Activities Profile
Groups	All
Purpose	To indirectly assess the overall aerobic cardiovascular fitness of the participant.
Equipment	Questionnaire & Pen
Procedure	For each activity, the participant ticks whether they are still doing, stopped doing or have never done it. The highest number activity reached is recorded. Please note that this profile is of American design and so I have translated distances etc into more understandable values.
Time	10 minutes
Recording	This will be a scannable document so the calculations are performed by the computer. FYI a maximum score and an adjusted score that discounts activities listed as never done is recorded.

(Daughton et al 1982)

Name	Grip Test
Groups	All
Purpose	To indirectly assess the strength of the quadriceps muscles.
Equipment	A hand dynamometer (Baseline; Fabrication Enterprises, Inc, White Plains, NY)
Procedure	<p>The participant will be sitting upright in a standard chair. The arm will be close to the side, in neutral rotation and the elbow flexed to 90°. The lower arm and wrist are in neutral position.</p> <p>The dynamometer will be held with its spine parallel to the participant's thumb. The dynamometer will be adjusted to suit the participant's hand size. The participant squeezes the dynamometer while keeping the wrist neutral and for 3 to 5 seconds. Pumping of the dynamometer is considered a failed trial as it may cause a false high reading. One warm up squeeze will be allowed and then the best of 2 trials will be recorded. A coin toss will decide which arm is tested first.</p> <p>NB it is recommended that batteries are removed between each assessment appointment.</p>
Time	5 minutes
Recording	Highest reading in kilograms to the nearest 0.1kg.

(Bohannon et al 2012; Burnstein et al 2011)

Name	Tecumseh Step Test
Groups	All
Purpose	To assess the aerobic capacity (fitness) of an individual.
Equipment	24 cm Step. Heart rate monitor. Metronome or music at 96 beats per minute.
Procedure	<p>Participants are asked to step up and down on to a 24cm step at a cadence of 24 steps or 96 beats per minute for 3 minutes. Either a metronome or music, as the participant prefers, will help guide the rhythm. The researcher will also count the beat if required. Both feet come to rest on to the box before stepping down. They may lead with either leg and swap during the test if they so choose. After finishing the test, the participant sits down immediately, resting and being as still as possible. Heart rate is taken for 30 seconds, 30 seconds after cessation of the test. Do not use a heart rate monitor as this give heart rate and not the number of beats in the set period.</p>
Time	5 minutes
Recordings	Number of heart beats in 30 seconds is the score.

(Montoye et al 1969)

Name	Foot & Ankle Ability Measure
Groups	All
Purpose	To assess the level of function pertaining to the ankle.
Equipment	Survey and pen
Procedure	Participants complete the survey. Tick box.
Time	4 minutes
Recordings	This is a scannable form. 2 scales: ADL & sport. Scored 0 – 84 on the ADL and 0 – 32 on sport. Scores are transformed in to percentages. Higher scores = greater function. There are additional global scores from single questions at the end of each scale scored out of 100. 0% = total inability. 100% = fully functional levels. Finally there is a categorical functional rating of 4 ratings of abnormal to normal.

(Martin et al 2005)

Name	Cumberland Instability Tool (CAIT)
Groups	All
Purpose	Validated too with cut off that assesses for the presence of ankle instability. A cut-off score of ≤ 27.5 indicates the presence of an unstable ankle. if participants are reporting bilateral symptoms the scores for both ankles must be calculated individually and the side with the worst score would be designated the affected side.
Equipment	Survey and pen
Procedure	Participants complete the survey.
Time	4 minutes
Recordings	This is a scannable form. Tick box. Scoring is somewhat complex & will be calculated when data in-putted. Each factor is scored 0 – 3, 4 or 5. Never scores receive 3 in Qs 8 & 9. A score of less than 27 has been determined as the cut-off point indicating instability.

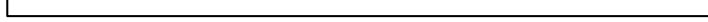
Please offer the participant some refreshment and check that they are feeling well post-testing.

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Physical Activity Survey (Occupation, Sport and Activity)

4, How active do you consider you have been in your main or longest lasting occupation?

Totally inactive. Always seated.	0		1	Extremely active and on my feet.
----------------------------------	---	--	---	----------------------------------

5, How much physical effort or energy has been needed to carry out your main or longest lasting occupation?

No real effort at all	0		1	Physically exhausting every day I work
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SECTION B. These questions are about exercise and physical activity.

6. If you have **never taken part in any** regular exercise at all please could you tell us why in the box below? Exercise and activities could include gym, walking more than 15 minutes, table tennis, volleyball, jogging, dancing, climbing, fencing, hiking, races in P.E. classes, paper round, go-karting. **PLEASE INCLUDE PLAYGROUND/PLAYING OUT PHYSICAL ACTIVITIES.**

If you have filled in question 6 you have now finished the survey. – Thank you!

Physical Activity Survey (Occupation, Sport and Activity)

8, For the 5 physical activities that you've spent most time doing, please can you answer the following questions. Feel free to ask the researcher questions.

Activity	How often did or do you take part?	Where did you take part? (school, club, park, gym, playground)	At what level did you take part? (casual, regular amateur, competitive amateur)	Did you ever have any injury due to the sport? (Yes or no)	If you had an injury, why do you think it happened? (Training error, collision with player, over did it etc)
1					
2					
3					
4					
5					

9, Thinking about the activity or sport that you have done the most. How did you learn how to do it? Please tick all that apply.

- Just did it
- Through magazines
- On-line/websites
- Sports at school
- Advice from friends
- Advice from haemophilia treatment centre
- Semi-professional trainer, coach or teacher
- Professional trainer or coach
- Other, please specify in the box below

11, Please tick all the exercise/training/activity surfaces that you have used.

- | | | | | | |
|--------------------------------|--------------------------|-----------------|--------------------------|-----------|--------------------------|
| Grass (level playing field) | <input type="checkbox"/> | Grass (uneven) | <input type="checkbox"/> | Dry slope | <input type="checkbox"/> |
| Paving (tarmac/concrete/stone) | <input type="checkbox"/> | Ice/snow | <input type="checkbox"/> | Astroturf | <input type="checkbox"/> |
| Other uneven surfaces | <input type="checkbox"/> | Sprung flooring | <input type="checkbox"/> | Water | <input type="checkbox"/> |
| Rubberised track | <input type="checkbox"/> | Wooden floors | <input type="checkbox"/> | None | <input type="checkbox"/> |
| Ash courts (tennis) | <input type="checkbox"/> | | | | |

12, Did your main exercise require protective equipment such as shin guards?

- Yes
- No If "no", go to Q 14.

Physical Activity Survey (Occupation, Sport and Activity)

13,

How often do you or did you wear the protective equipment required by your chosen sport/activity?

0

1

Never

Always

14, Do you ever have minor injuries to your joints that you don't mention to anyone such as minor sprains?

Yes

No

15, Please would you tell us why you didn't tell anyone?

Physical Activity Survey (Occupation, Sport and Activity)

16, As a child, do you remember playing the same games as your friends?

- Yes
- No
- Don't remember
- Don't know

17, Were there certain games that you weren't allowed to play?

- Yes If, yes – please write what they were in the box below.
- No
- Don't remember

18. As a child, how did you get to take part in your sports and physical activities? You can tick more than one box.

- My parents picked them for me
- My parents and doctors/nurses/physio picked them
- My doctors/nurses and physios picked them
- I was involved in deciding with others
- There were things that my school didn't allow me to do
- I chose what I wanted to do

Physical Activity Survey (Occupation, Sport and Activity)

19, Overall, do you feel that you ran around more, the same or less than your friends when you were 5 years old?

- Same
- More
- Less
- Can't remember

20, And at 10 years old?

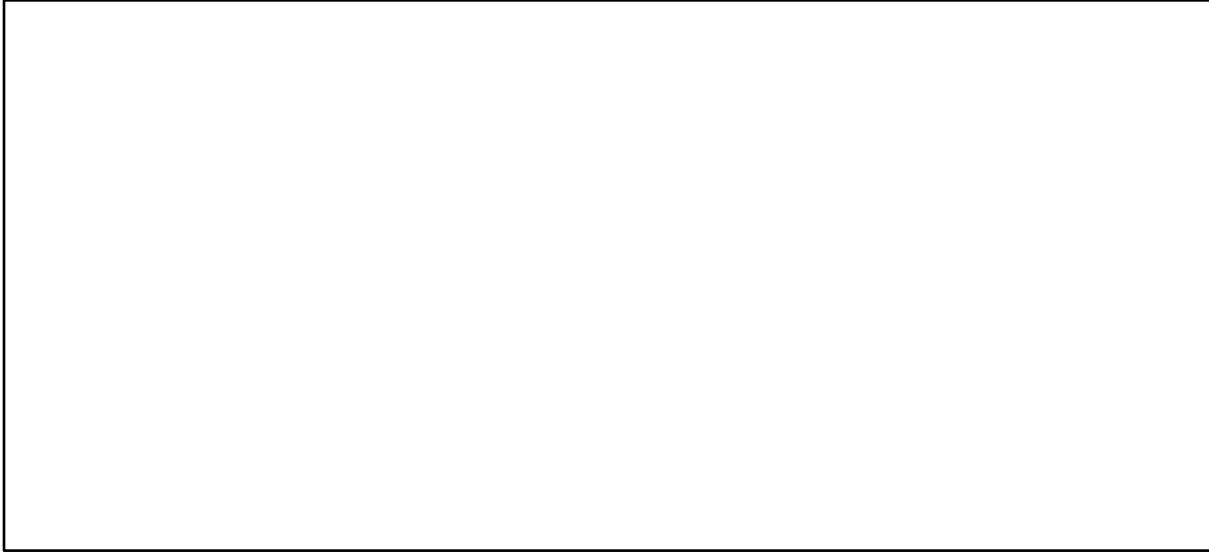
- Same
- More
- Less
- Can't remember

21, And at 15 years old?

- Same
- More
- Less
- Can't remember

Physical Activity Survey (Occupation, Sport and Activity)

22. Is there anything else about occupation, sport and exercise that you think might be important that we haven't asked?



Thank you very much for completing this survey!

E Appendix 30 Activity Questionnaire Non Haemophilia Young Person

Date:

Participant No.:

Dear Participant,

We are interested in knowing about how active you are now and, if possible, in the past. There are also some questions about injury and recovery. Please answer as much as you can.

1. When did you finish your education? Please tick the box that applies to you.

I'm still studying

Left school before 16

Left school at 16

Left school at 18

2. If you have **never taken part in any** regular exercise please could you tell us why in the box below?

Exercise and activities could include gym, walking more than 15 minutes, table tennis, volleyball, jogging, dancing, climbing, fencing, hiking, races in P.E. classes, paper round, go-karting. **PLEASE INCLUDE PLAYGROUND/PLAYING OUT PHYSICAL ACTIVITIES e.g. chasing games.**

If you have filled in question 2 you have now finished the survey. – Thank you!

3. Please list any sports or other physical activities you have taken part in regularly including casual games with friends and playground games. Also include daily activities such as walking. Please **tick** the boxes to indicate how old you were for each sport/activity and how many years you took part.

Activities ↓	Age →	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
E.g Playground football								✓	✓	✓	✓	✓	✓	✓				

Activities could include: gym, walking more than 15 minutes, table tennis, volleyball, jogging, dancing, climbing, fencing, hiking, races in P.E. classes, paper round, go-karting. **PLEASE INCLUDE PLAYGROUND/PLAYING OUT PHYSICAL ACTIVITIES.**

4, For the 5 physical activities that you've spent most time doing, please can you answer the following questions. Feel free to ask the researcher questions.

Activity	How often did or do you take part?	Where did you take part? (school, club, park, gym, playground)	At what level did you take part? (casual, regular amateur, competitive amateur)	Did you ever have any injury due to the sport? (Yes or no)	If you had an injury, why do you think it happened? (Training error, collision with player, over did it etc)
1					
2					
3					
4					
5					

5. Thinking about the activity or sport that you have done the most. How did you learn how to do it? Please tick all that apply.

- Just did it
- Through magazines
- On-line/websites
- Sports at school
- From friends
- Advice from haemophilia treatment centre
- Semi-professional trainer or coach
- Professional trainer or coach
- Other, please specify in the box below

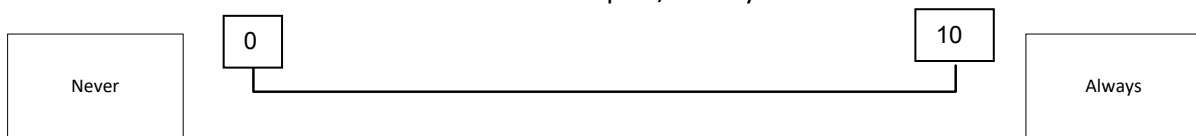
6. Please tell us what kind of exercise/training surfaces you have used. Tick as many as you like.

- | | | |
|---|--|------------------------------------|
| Grass (level playing field) <input type="checkbox"/> | Grass (uneven) <input type="checkbox"/> | Dry slope <input type="checkbox"/> |
| Paving (tarmac/concrete/stone) <input type="checkbox"/> | Ice/snow <input type="checkbox"/> | Astroturf <input type="checkbox"/> |
| Other uneven surfaces <input type="checkbox"/> | Sprung flooring <input type="checkbox"/> | None <input type="checkbox"/> |
| Rubberised track <input type="checkbox"/> | Wooden floors <input type="checkbox"/> | |
| Ash courts (tennis) <input type="checkbox"/> | Water <input type="checkbox"/> | |

7. Did your favourite sport/activity require you to wear protective gear such as shin guards?

- Yes
- No If not, go to Q 9

How often you did or do you wear the protective gear needed for your chosen sport/activity?



8.

9. Do you ever have minor injuries from your sports or physical activities that you don't mention to anyone such as sprains?

Yes
No

10. Please could you tell us why you didn't tell anyone?

11.

When you tell your hospital support team about a bleed or injury, are you offered exercises or stretches to do at home to help you get better?

Never 0 10 Always

12.

How well did you stick to instructions when you were given exercises or stretches to do at home by your clinical support team?

Never Always

0 10

13. If you have ever chosen not to carry out exercises suggested to you by your haemophilia centre, would you please tell us why? It can be just a single word answer.

14. Outside of school, do you play the same games and sports as your friends? Please tick the box that applies to you.

- Yes
- No
- Don't remember
- Don't know

15. Are or were there certain games that you aren't/weren't allowed to play because it was thought that they might not be a good idea for you? – either at home or at school.

- Yes If, yes – please write what they were in the box below.
- No
- Don't remember
- Don't know

16. How did you get to take part in your sports and physical activities? You can tick more than one box.

- My parents picked them for me
- My parents and doctors/nurses/physio picked them
- My doctors/nurses and physios picked them
- I was involved in deciding with others
- There were things that my school didn't allow me to do
- I chose what I wanted to do

17. On the whole, do you feel that you ran around more, the same or less than your friends when you were 5 years old? Please tick the box that applies to you.

- Same
- More
- Less
- Can't remember

18. And at 10 years old?

- Same
- More
- Less
- Can't remember

19. And at 15 years old?

- Same Not applicable
- More
- Less
- Can't remember

20. And now?

- | | | | |
|----------|--------------------------|----------------|--------------------------|
| Same | <input type="checkbox"/> | Not applicable | <input type="checkbox"/> |
| More | <input type="checkbox"/> | | |
| Less | <input type="checkbox"/> | | |
| Not sure | <input type="checkbox"/> | | |

21. Is there anything else about sport and exercise that you think might be important to how haemophilia affects you that we haven't asked?

Thank you very much for completing this survey!

E Appendix 31 Activity Questionnaire NonHaemophilia Young Person

Date:

Participant No.:

Dear Participant,

We are interested in knowing about how active you are now and, if possible, in the past. There are also some questions about injury and recovery. Please answer as much as you can.

1. When did you finish your education? Please tick the box that applies to you.

I'm still studying

Left school before 16

Left school at 16

Left school at 18

2. If you have **never taken part in any** regular exercise please could you tell us why in the box below?

Exercise and activities could include gym, walking more than 15 minutes, table tennis, volleyball, jogging, dancing, climbing, fencing, hiking, races in P.E. classes, paper round, go-karting. **PLEASE INCLUDE PLAYGROUND/PLAYING OUT PHYSICAL ACTIVITIES e.g. chasing games.**

If you have filled in question 2 you have now finished the survey. – Thank you!

3. Please list any sports or other physical activities you have taken part in regularly including casual games with friends and playground games. Also include daily activities such as walking. Please **tick** the boxes to indicate how old you were for each sport/activity and how many years you took part.

Activities ↓	Age →	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
E.g Playground football								✓	✓	✓	✓	✓	✓	✓				

Activities could include: gym, walking more than 15 minutes, table tennis, volleyball, jogging, dancing, climbing, fencing, hiking, races in P.E. classes, paper round, go-karting. **PLEASE INCLUDE PLAYGROUND/PLAYING OUT PHYSICAL ACTIVITIES.**

4, For the 5 physical activities that you've spent most time doing, please can you answer the following questions. Feel free to ask the researcher questions.

Activity	How often did or do you take part?	Where did you take part? (school, club, park, gym, playground)	At what level did you take part? (casual, regular amateur, competitive amateur)	Did you ever have any injury due to the sport? (Yes or no)	If you had an injury, why do you think it happened? (Training error, collision with player, over did it etc)
1					
2					
3					
4					
5					

Sport and Activity Survey for People Aged 12 - 18

5. Thinking about the activity or sport that you have done the most. How did you learn how to do it? Please tick all that apply.

- | | |
|--|--------------------------|
| Just did it | <input type="checkbox"/> |
| Through magazines | <input type="checkbox"/> |
| On-line/websites | <input type="checkbox"/> |
| Sports at school | <input type="checkbox"/> |
| From friends | <input type="checkbox"/> |
| Advice from haemophilia treatment centre | <input type="checkbox"/> |
| Semi-professional trainer or coach | <input type="checkbox"/> |
| Professional trainer or coach | <input type="checkbox"/> |
| Other, please specify in the box below | <input type="checkbox"/> |

6. Please tell us what kind of exercise/training surfaces you have used. Tick as many as you like.

- | | | | | | |
|--------------------------------|--------------------------|-----------------|--------------------------|-----------|--------------------------|
| Grass (level playing field) | <input type="checkbox"/> | Grass (uneven) | <input type="checkbox"/> | Dry slope | <input type="checkbox"/> |
| Paving (tarmac/concrete/stone) | <input type="checkbox"/> | Ice/snow | <input type="checkbox"/> | Astroturf | <input type="checkbox"/> |
| Other uneven surfaces | <input type="checkbox"/> | Sprung flooring | <input type="checkbox"/> | None | <input type="checkbox"/> |
| Rubberised track | <input type="checkbox"/> | Wooden floors | <input type="checkbox"/> | | |
| Ash courts (tennis) | <input type="checkbox"/> | Water | <input type="checkbox"/> | | |

7. Did your favourite sport/activity require you to wear protective gear such as shin guards?

- Yes
- No If not, go to Q 9

8.

How often you did or do you wear the protective gear needed for your chosen sport/activity?

Never	0		1	Always
-------	---	--	---	--------

9. Do you ever have minor injuries from your sports or physical activities that you don't mention to anyone such as sprains?

Yes

No

10. Please could you tell us why you didn't tell anyone?

11. Outside of school, do you play the same games and sports as your friends? Please tick the box that applies to you.

Yes

No

Don't remember

Don't know

12. Are or were there certain games that you aren't/weren't allowed to play because it was thought that they might not be a good idea for you? – either at home or at school.

Yes

If, yes – please write what they were in the box below.

No

Don't remember

Don't know

13. How did you get to take part in your sports and physical activities? You can tick more than one box.

My parents picked them for me

My parents and doctors/nurses/physio picked them

My doctors/nurses and physios picked them

I was involved in deciding with others

There were things that my school didn't allow me to do

I chose what I wanted to do

14. On the whole, do you feel that you ran around more, the same or less than your friends when you were 5 years old? Please tick the box that applies to you.

- Same
- More
- Less
- Can't remember

15. And at 10 years old?

- Same
- More
- Less
- Can't remember

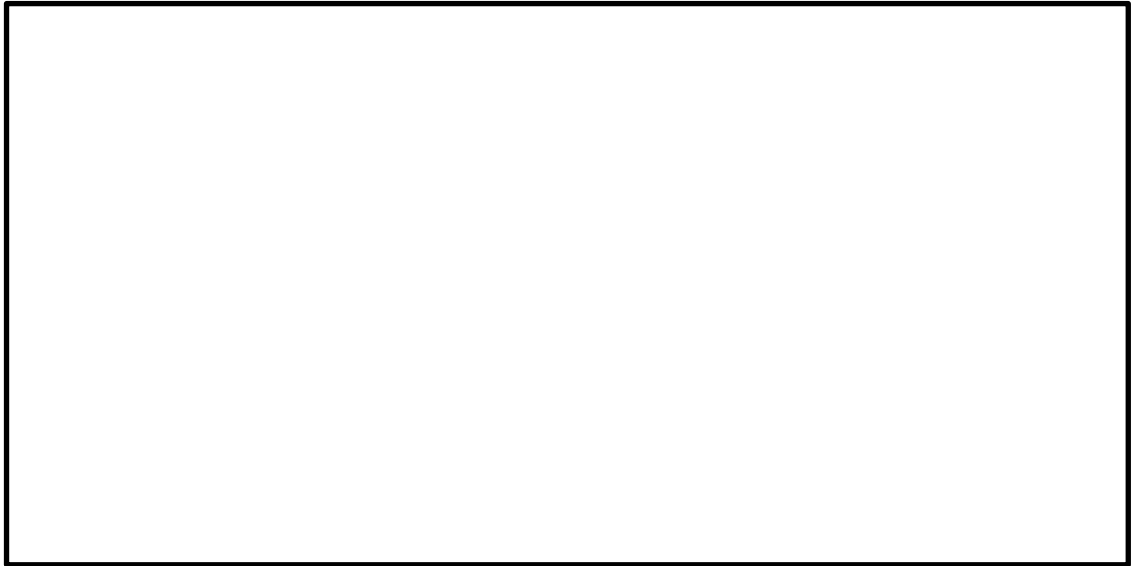
16. And at 15 years old?

- Same Not applicable
- More
- Less
- Can't remember

17. And now?

- Same Not applicable
- More
- Less
- Not sure

18. Is there anything else about occupation, sport and exercise that you think might be important that we haven't asked?



Thank you very much for completing this survey!