Development and preliminary evaluation of an exercise-based telerehabilitation intervention for people with severe haemophilia: a mixed methods study

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Declaration

I, Paul McLaughlin, confirm that the work presented in this thesis is my own, except where reference has been made to the published literature.

Signed: 

Statement from funder

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Working in haemophilia is a privilege, and I am fortunate to work with the most amazing bunch of haematologists, clinical nurse specialists, physiotherapists, healthcare assistants, laboratory scientists, haemophilia research and administration teams, surgical and radiology colleagues. My thanks to them for their patience and support in my more hectic moments.

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Dissemination

Publications

- McLaughlin P, Hurley M, Chowdary P, Khair K, Stephensen D. Physiotherapy interventions for pain management in haemophilia: A systematic review. Haemophilia 2020. 26 (4); 667-684.
- McLaughlin P, Hurley M, Chowdary P, Stephensen D, Khair K. How does a lifetime of painful experiences influence sensations and beliefs about pain in adults with severe haemophilia? A qualitative study. Disability and Rehabilitation 2021, doi.org/10.1080/09638288.2021.2018053
- McLaughlin P, Hurley M, Chowdary P, Stephensen D, Khair K. The experiences and beliefs of people with severe haemophilia and healthcare professionals on pain management, and their views of using exercise as an aspect of intervention: a qualitative study. 2021, Disability and Rehabilitation doi.org/10.1080/09638288.2021.2018054

Invited talks

- Oral presentation at the annual UK Haemophilia Chartered Physiotherapists Association meeting, Birmingham, March 2019. Physiotherapy interventions for pain management in haemophilia: early results of systematic review.
- Roundtable symposia and oral presentation - European Haemophilia Consortium (EHC) Roundtable of Stakeholders on Pain Management in Haemophilia. Host: EHC, Brussels, June 2019. Presentation – overview of pain management in haemophilia as part of a multi-professional faculty.
- Oral presentation at the South London Health Innovation Network MSK Improvement and Innovation forum, London, October 2019. Overview of haemophilia and my PhD research
- Oral presentation for the European Haemophilia Consortium Virtual conference, October 2020. Co-presenting on a session with a Belgian colleague and two people with bleeding disorders - pain management and physiotherapy.

- Oral presentation to the Northern Ireland Haemophilia centre (virtual), November 2020 – The childhood experience of pain – does it influence pain beliefs in adults with haemophilia? Findings of qualitative study.
- Guest speaker on 'Haemcast' (A podcast series for haemophilia and other bleeding disorders), Feb 2021. Titled 'We don't ask, they don't tell – pain in haemophilia'.
- Oral presentation to the Complex pain team at University College London Hospital, March 2021. The development of a novel pain management intervention for people with haemophilia.
- Oral presentation – webinar by invitation of the National Hemophilia Foundation (USA), April 2021. Pain and problem joints in haemophilia
- Oral presentation to the Australian Haemophilia Physiotherapists specialist interest group, October 2021. Pain management in haemophilia and the current evidence for physiotherapy.
- Oral presentation to the annual Australian Haemophilia Foundation Annual congress, October 2021. Overview of pain management in haemophilia.
- Oral presentation to the Post Graduate Research Group at St George's University, January 2022. Stakeholder involvement in the development of a novel pain management intervention for people with haemophilia.

Poster presentations/ Conference presentations

- ‘Rapid 5’ oral presentation at ‘Physiotherapy UK’ annual congress, Nov 2019. Physiotherapy interventions for pain management – a systematic review.
- Poster presentation at the World Federation of Hemophilia World congress, May 2021. Haemophilia, pain and exercise: conflict, control and uncertainty. The views, beliefs and experiences of people with haemophilia and healthcare professionals: a qualitative study
- Poster presentation at the NIHR academy members conference, November 2021. Stakeholder involvement in the design and delivery of a novel telerehabilitation intervention for pain management in people with haemophilia
- Oral presentation at EAHAD congress, Feb 2022. Stakeholder involvement in the development of a programme theory for a novel physiotherapy intervention for pain management in haemophilia

Awards

I was the recipient of the British Society of Haematology and NIHR AHP/Nurse Researcher of the year award, April 2022.

Abstract

Background: Haemophilia is a rare and lifelong bleeding disorder. In its untreated state it is associated with musculoskeletal bleeding, which leads to the development of painful haemophilic arthritis. Chronic pain associated with arthritis is reported by between 30-71% of people with haemophilia (PWH), yet there remains limited guidance on management approaches, including physiotherapy. It is unclear if an approach using exercise could be effective or acceptable to PWH.

Methods: In keeping with the Medical Research Council's framework for developing complex interventions, an extensive literature review and a qualitative study with PWH and healthcare professionals identified key uncertainties in the current evidence base. A stakeholder-informed theory of change approach that integrated behavioural theory, created a programme theory. This informed the development of a novel, mixed methods, exercise based, telerehabilitation intervention for use in people with severe haemophilia and chronic pain.

Results: The systematic review found low quality of evidence of effect for physiotherapy interventions on pain, function, and quality of life. The qualitative study highlighted that pain existed in an uneasy coalition with haemophilia, PWH wanted support to be able to do more despite their pain, and exercise as an approach was broadly acceptable. The programme theory identified key enablers, activities and behaviour change techniques likely to achieve the outcomes of the study. Ten PWH participated in a multi-site, non randomised study with a nested semi-structured interview. Over 6 weeks, a real time telerehabilitation intervention was delivered using the MS Teams platform by specialist haemophilia physiotherapists known to the participants. The mixed method data analysis confirmed that the intervention was feasible, acceptable, and safe for PWH.

Conclusions: This thesis adds to understanding of the pain experiences in PWH. It furthers the evidence base for non-medical approaches for pain management in PWH and has identified areas of future research need.

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List of Abbreviations

BCT's	Behaviour Change Techniques
BCW	Behaviour Change Wheel
BPI	Brief Pain Inventory
CFC	Clotting Factor Concentrate
CERT	Consensus in Exercising Reporting Template
COM-B	Capability, Opportunity, Motivation- Behaviour
CRF	Case Report Form
EULAR	European League Against Rheumatism
HAL	Haemophilia Activities List
HCV	Hepatitis C Virus
HILT	High Intensity Laser Therapy
HIV	Human Immuno-deficiency Virus
MCID	Minimal Clinically Important Difference
MMR	Mixed Methods Research
MRC	Medical Research Council
MS	Microsoft
MSK-HQ	Musculoskeletal Health Questionnaire
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NSAID's	Non Steroidal Anti-inflammatory Drugs
OA	Osteoarthritis
PEMF	Pulsed Electro Magnetic Field
PIS	Participant Information Sheet
PROBE	Patient Reported Outcomes, Burdens and Experiences
PROM	Patient Reported Outcome Measure
PSEQ	Pain Self-Efficacy Questionnaire
PWH	People/person with haemophilia
PWModH	People/person with moderate haemophilia
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial

ToC	Theory of Change
VAS	Visual Analogue Scale
WFH	World Federation Of Hemophilia

Preface

I have been working as a specialist physiotherapist in field of haemophilia care for 16 years. The desire to undertake the programme of research described in this thesis was driven by my observed clinical experiences, as well as the views and input of the people with haemophilia that I worked with day to day. Seeing the struggles for many living with chronic pain helped drive forward the need to investigate the potential of an exercise based rehabilitation approach. Albeit one that would require some certainty of safety, as well as an approach that was acceptable to people with haemophilia. On commencing the PhD programme in June 2018, it was envisaged that the method of delivery of the rehabilitation programme would most likely be that of a face to face intervention based within NHS physiotherapy department gymnasiums.

Early 2020 saw the emergence of the Covid-19 global pandemic. This had an immediate, serious, and significant impact on the provision of health care services and research activity. In March 2020, I was in the final stages of data analysis for the qualitative study presented in Chapter 4, and making initial plans for convening the stakeholder group to take part in the theory of change development described in Chapter 5. As with many other clinical researchers, I had to pause my research and return full time to support acute clinical services within the hospital. This hiatus lasted three months. Although I was initially concerned about a negative effect of the time away from qualitative data analysis, it retrospect this was actually beneficial. I returned to the dataset anew which helped me see the data with fresh eyes and develop my analysis for the better.

Whilst the first initial peak of Covid-19 eased towards the latter end of 2020, there remained limitations on social contact both in and out of hospital environments. Risk of covid transmission and ongoing social distancing requirements at the time meant that theory of change stakeholder workshop had to be convened online. More pressing however, was the need for my research team and I to consider the best mode of delivery of the rehabilitation intervention. Whilst there appeared to be some easing of restrictions in respect of social contact and healthcare provision, there remained a great deal of uncertainty as to what future health and social limitations may or may not be in place (considering the time needed for the ethical approval process). The

research team discussed at length the pro's and con's of in person face to face, fully virtual or blended delivery approaches. The decision was made at to proceed with an intervention that would require one initial face to face session followed by real time, virtual telerehabilitation sessions. Even so, at this point there remained issues across the NHS with consistent access to technology such as video-conferencing platforms and hardware such as webcams and microphones. There was an acknowledged element of risk in planning a virtual intervention and not being sure the technology could/would work, or if the study could be done. Time and financial restrictions associated with my fellowship also meant that only the consent form had the option of being digitised for electronic signing. The included outcome measures were all kept as paper copies.

I did not envision the inclusion of digital health strategies when starting my PhD. However, the exceptional set of challenges presented by the Covid 19 pandemic, and the resultant adaptations challenged me in a myriad of ways. I feel I have shown resilience in these circumstances and, more positively, demonstrated the feasibility of telerehabilitation as a potential delivery option in a post covid era.

In describing the unique set of events in which this thesis was conducted, I provide context and explanation for the choices made. I ask those who read this thesis to consider and appreciate this unique set of circumstances when reading the work presented.

Chapter 1 - Introduction

This chapter will present an overview of haemophilia in the context of its prevalence, clinical signs and symptoms, medical management and the co-morbid issue of joint disease related with the disorder. The burden associated with haemophilic arthropathy will be discussed with a focus on the development of chronic pain and its effect on those who live with it, as well as a review of physiotherapy approaches in haemophilia. The chapter concludes by highlighting the limitations of current approaches for pain management in people with haemophilia and how this has informed the aims and objectives for the study presented in this thesis.

1.1 Definition of haemophilia

Haemophilia is the umbrella term for the most common of the rare lifelong bleeding disorders – haemophilia A (deficiency of clotting factor protein VIII) and haemophilia B (deficiency of clotting factor protein IX). Both disorders occur due to a mutated or absent genetic code on the X chromosome, and because of this is X-linkage, it almost exclusively affects males (1, 2). The presence of adequate factor VIII and IX is central to the process of normal blood coagulation. They enable the generation of sufficient thrombin to stop bleeding and permit adequate healing to take place (3).

1.1.1 Diagnosis

Presentation for medical care is often initiated because of a known family history of haemophilia, or because of symptoms of unexplained bleeding. Clinical diagnosis of either disorder is confirmed with a specific laboratory factor assay, whereby severity of the disease is then established. This classification has three stages (mild, moderate, severe) and is based against normal values for clotting factors of 50-150%. Mild haemophilia is where clotting factor levels are between 5-40% of normal, moderate has levels between 1-4% of normal and severe with levels of <1% of normal (4, 5).

1.1.2 Incidence

Both haemophilia's occur in all racial groups and are found worldwide. The global prevalence of haemophilia A is estimated to be 17.1 cases per 100,000 males (with 6/100,000 being severe), compared to the much rarer haemophilia B figure of 3.8 cases per 100,000 males (with 1.1/100,000 being severe) (6). Approximately 10,686

people with haemophilia A or B are currently registered in the UK, of which 32% are classified as having a severe or moderate diagnosis of the disorder (7).

1.2 Clinical presentation

In its untreated state spontaneous bleeding into the muscle and joints is the hallmark of severe haemophilia and most children with severe haemophilia have their first bleed by the age of 4 years old (4). Retrospective data analysis from a large cohort of children in the United States confirmed that 81% experienced their first bleed by the age of 2 years, and that 84% of those episodes were musculoskeletal in nature (8). It is widely agreed that this bleeding pattern increases as baby mobility increases, and highlights the early exposure to pain related to bleeding that babies born with severe haemophilia may experience.

People with moderate haemophilia (PWModH) also experience traumatic and spontaneous musculoskeletal bleeding episodes, though for many years the clinical assumption was they did not bleed as often as those with severe disease. However, increasing data highlights that moderate haemophilia may well be a neglected disorder in respect of musculoskeletal bleeding. Recent reports indicate that PWModH may have the same number of joint bleeds per year as those with severe disease and that some 43% and 15% of PWModH report joint impairment and chronic pain respectively (9).

The definition of mild haemophilia is broader in comparison to moderate and severe due the wider range of circulating plasma factor levels attributed to it (5-40% of normal). As a result of the presence of some clotting factor protein in the circulation, bleeding episodes are rarer and usually characterised by trauma (5). People with mild haemophilia usually have minimal joint/musculoskeletal involvement as the number of joint bleeds decreases as plasma factors levels increase (10). The minimal level of clotting factor protein needed to prevent any bleeding (excluding serious trauma/surgery) has been estimated in one study at 12% (11) but as high as 30% in another (10). Whatever the level of deficiency, there is large variability in bleeding patterns on both an individual level and at a disease population level. Such variances bring into question the traditional classification model based on mild, moderate or

severe (12) and highlights the need for an individual approach to medical treatment with replacement therapy.

1.3 Haemophilia treatment history

Following the end of the Second World War, management of haemophilia had advanced little, with immobilisation of swollen, painful joints being the main treatment (13). In the 1950's/1960's it was common to see signs stating 'No Aspirin, No injections, No exercise' above the beds of those hospitalised with joint bleeding (14). It was not until the discovery of cryoprecipitate (a concentrated subset of clotting proteins filtered from whole blood) in 1965, that treatment was revolutionised and more effective treatment of bleeding episodes could be achieved (15). However, this human blood product brought its own risks, and in the late 1970's and early 1980's many PWH were coinfected with hepatitis and HIV. Recombinant factor replacement eventually came to market in the late 1980's and has been the treatment of choice until very recently.

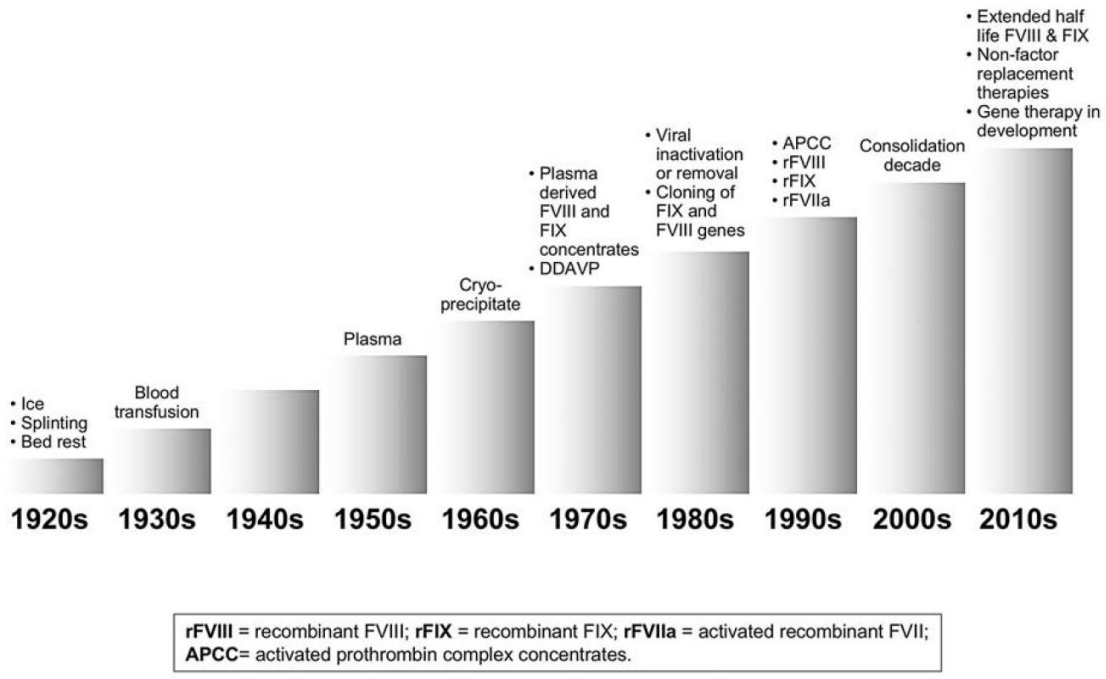


Figure 1: Timeline of development of haemophilia treatment (From Mannucci 2020) (16)

Extended half-life recombinant factor products and non-factor treatments for PWH have been developed with the aim of increasing overall protection from bleeding and decreasing the burden associated with regular intravenous injections. Extended half-life factor concentrates are bioengineered molecules that have a prolonged plasma half-life of between 1-3 times that of standard concentrates (17). They are still delivered intravenously. Non-factor replacement therapies are also bioengineered molecules but developed to be delivered via subcutaneous injection. Some are humanised bispecific monoclonal antibodies that mimic the functions of activated FVIII. Others seek to rebalance haemostasis by targeting natural inhibitors of the coagulation cascade (18). Gene therapy offers the promise of a functional cure for both Haemophilia A and B, although it remains in clinical trial development. Currently there remains limited data on musculoskeletal outcomes when using these novel treatments and so ongoing evaluation is required.

1.3.1 Rationale for current treatment approaches

The mainstay of modern treatment is to raise the factor levels in the blood or balance haemostasis enough so as to limit the possibility of spontaneous bleeding (4). Depending on the severity of the disease, this is directed at either trying to prevent bleeding from happening (referred to as prophylaxis; primary, secondary, or tertiary), or to treat as soon as possible after a bleeding event has occurred (referred to as episodic or On-demand treatment) (Table 1) (19)

The rationale behind the application of prophylaxis stemmed from observations that those with moderate or mild forms of haemophilia did not appear to bleed as often as those with severe haemophilia. In 1958 this led a Swedish medical team to treat PWH regularly with regular small amounts of clotting factor replacement, with the aim of ensuring their trough levels (the measurable amount of factor concentrate in their blood) did not drop below 1% for long periods of time. The observations from these studies confirmed that such an approach led to less bleeding episodes and ultimately less physical disability from musculoskeletal bleeding (20).

Table 1: The International Society for Thrombosis and Haemostasis (ISTH) description of prophylaxis provision

Primary prophylaxis	Begins in early childhood in the absence of joint disease and before the second clinically evident joint bleed – before the age of three. PWH in this category would be expected to look forward to a normal life with minimal risk of arthropathy
Secondary prophylaxis	Commences after 2 or more bleeds, but before the onset of joint disease as documented by physical examination and/or imaging. PWH in this category may already have a significant risk of developing arthropathy
Tertiary prophylaxis	Treatment initiation after the onset of joint disease at any age. The objectives for treatment here would be to slow down progression of joint disease, reducing pain and inflammation and the maintenance of mobility

Even with the obvious benefits of regular factor replacement, it was not until 2007 that the seminal study by Manco-Johnson and colleagues provided the evidence of efficacy of a primary prophylaxis approach for children with haemophilia (21). In their RCT, 65 boys with haemophilia (FVIII level <2%) with a mean age of 1.6 years, were randomised to a prophylaxis arm (25iu/Kg alternate days) or an episodic arm (acute bleed initial treatment 40iu/kg). Joint health was evaluated using MRI and plain film X-ray. Forty-six participants completed the protocol. On follow up when 6 years old, normal joint MRI findings were reported for 93% of the prophylaxis group and 55% of the episodic treatment group, with the episodic group also reporting more bleeds than the prophylaxis group. Their findings highlighted an 83% decrease in the risk of haemophilia related joint damage for the group on prophylaxis compared to episodic treatment. Another Italian study compared the same treatment approach but with less frequency of prophylaxis (three times per week) and slightly smaller factor concentrate dosages for bleeding episodes. Similar to Manco-Johnson, X-Ray evidence of joint damage was seen in 29% of those on a prophylaxis arm and 74% on the episodic treatment arm (22). Interestingly both papers found no significant correlation between number of joint haemorrhages and radiological changes in joint health, suggesting a subclinical process resulting in joint deterioration without explicit clinically evident joint bleeding.

Providing regular treatment to those PWH who have existing joint disease is referred to as tertiary prophylaxis, with the main aim being to prevent bleeding so as to lessen the speed of progression of joint disease (19). The efficacy of a tertiary prophylaxis regime in adults with severe haemophilia A was investigated by Collins et al (2010)(23). Nineteen people (aged 30-45) took part in a cross over study where they used episodic treatment for the first six months and prophylaxis (20-40iu/Kg) for the following seven months. The most affected joints were the elbow, followed by the ankle, then the knee, and 80% of participants had more than one affected joint. Treatment for acute bleeding was recorded by 89.8% of participants in the initial six months, falling significantly to 3.2% in the following six months on prophylaxis. Whilst there were remarkable changes in bleeding, the authors found no change in pain (as measured by the Gilbert Score) or quality of life. A retrospective observational cohort study of adolescent and adult PWH in 10 Italian haemophilia centres found similar decreases in bleeding events after 84 PWH switched from on-demand treatment to prophylaxis. However, in contrast to Collins et al, they found significant improvements in pain and quality of life after the switch (as measured by the EQ5D) but also no change on X-ray of joints after switching (24). It is worth noting however that the Italian cohort had all been on prophylaxis for at least two years, compared to six months in the Collins paper. A RCT investigating the influence of tertiary prophylaxis (versus on-demand treatment) on joint status found that quality of life, pain and physical activity improved with a reduction in the bleeding episodes. Whilst joint status as assessed by physical joint assessment improved in the prophylaxis cohort, joint health assessed by MRI of both groups got worse (25).

Treatment approaches using regular prophylaxis are only available to counties that have a healthcare budget to support its provision and as such many PWH only have access to bleed related episodic treatment. A 5-year longitudinal study evaluated musculoskeletal outcomes in children using episodic treatment across nine developing countries (26). They reported that the cohort had a median annualised bleed rate of 10 per year, with this figure being higher in older children. Physical assessment scores of affected joints (elbow, knee, ankle) and functional assessments worsened during the study, and X-ray changes were more significant in those that had more than five bleeds per year. The authors highlight that it was bleed frequency rather than access to

clotting factor concentrates that seems to most affect musculoskeletal outcomes, again highlighting the importance of prophylaxis for joint health. A recent systematic review evaluating the long-term outcomes of prophylaxis highlighted better joint health outcomes in children in countries that used early prophylaxis. Those countries with the longest time using prophylaxis (from 1997-2006) were demonstrating 50% of people with no joint damage, compared to 19% in those with starting later with prophylaxis availability (2007-), and those children on prophylaxis had a median annual joint bleed rate of 2.1 compared to 12 in those with only episodic treatment available (27).

The research in this area highlights that even with significant bleed reduction joint health may continue to decline (radiologically), providing further evidence for the importance of early and sustained prophylaxis in PWH. It also points to the complexities associated with what may be contributing to an individual's overall physical health, bleed state, pain, and function.

1.4 Musculoskeletal Bleeding

Musculoskeletal bleeding, predominantly into articular joints, is a hallmark symptom of haemophilia (4, 28). This process of recurrent articular bleeding is one of the most disabling features of the condition. However, there are variances even within a diagnosis of severe haemophilia. Depending on the phenotypic severity of bleeding, the age for the first joint bleed has been described between 0.2 months and 5.8 years (29), between 17-26.4 months (21, 30) or more broadly by the age of four years old (4). Such discrepancy has wide ranging implications as the milder phenotype also suggests a requirement for less factor replacement concentrate as well as less arthropathy in the years following the first bleed onset (29).

This phenomenon of intra-articular joint bleeding in haemophilia is proposed to initiate the process of the joint health destruction in 3 broad, but interrelated, stages (31):

1. Acute haemarthrosis
2. Joint synovitis
3. Degenerative haemophilic arthropathy

1.4.1 Acute Haemarthrosis

A haemarthrosis (bleeding into a joint) predominantly occurs in large synovial joints, with the bleed source being attributed to the synovial layer itself (32). The exact mechanism by which a bleed is provoked remains unknown, with the best working theory being that the synovial lining gets squashed or nipped between two opposing joint surfaces (28). This in turn causes vascular damage to the synovial lining allowing blood to flow directly into the articular space.

Rapid onset pain, swelling, limited range of movement, palpable heat and inability to weight-bear (for joints of the lower limb) are classical symptoms of an acute haemarthrosis (19). Many PWH describe a tingling or aura-like sensation in the joint as bleeding starts. Bleeding will continue until the pressure within the joint space is so great that it tamponades, or until clotting factor concentrates are infused.

Time to resolution of the joint haemorrhage is lengthy and relies on minimal mechanical stress to the affected joint as well as sufficient clotting factor treatment to facilitate healing (if available). It has been postulated that it can take up to 4 weeks for the intra-articular blood to be removed from the joint, and this process relies on a synovial layer that is not overwhelmed by the pathophysiological process at play (33).

1.4.2 Joint Synovitis

Synovial membrane covers all non-articular regions where movement occurs, and in a joint it lines the inside of the capsule and covers exposed osseous surfaces, intracapsular ligaments, bursae, and tendon sheaths. Healthy synovium is 1-3 cell layers thick, pink, smooth and shining, with villi normally noted near articular margins and on surfaces of folds or margins. These villi may be a functional design to allow an increased surface area to help distribute the lubricating synovial fluid over the articular surface (34).

Synovial tissue has a very specific composition relating to its main functions of joint lubrication, nutrition, and removal of joint debris. Two cell types exist in this thin layer. Type A cells are mostly macrophages, which release lytic enzymes and phagocytose joint debris. The Type B cells moderate this action by releasing enzyme inhibitors, as well as producing specialised fibroblasts, hyaluronan and glycoproteins into synovial fluid for nutrition (35). Synovial fluid is mainly dialysate of blood plasma and has both

viscoelastic and thixotropic properties. The lining rests on a fibrovascular sub intima which is highly vascularised. The small capillaries and lymphatic vessels enable small molecules to pass to and from the joint space to maintain nutrition (34).

The vascular bed in the sub-lining of synovium is the source of intra-articular joint bleeding in haemophilia. In an initiating haemarthrosis the synovial tissue will be able to clear the blood product and over time return to a relatively healthy state. In haemophilia however, a single bleeding event is rarely the case and repeated bleeding events occur. If bleeding continues and three or more events occur within the same joint within a six month period it is known as a target joint (19).

The presence of an increased amount of intra-articular blood is a physiological trigger for the synovial tissue. The synovium has the ability to upregulate cells involved in iron processing and regulation (36), which aims to provide homeostasis to the joint space. However, it has been noted that the vascular changes in the synovium even at this early stage may be irreversible(28). Iron is released as haemoglobin is broken down and due to its highly pro-inflammatory nature, it potentiates hypertrophy and hyperplasia of synoviocytes alongside hypervascularisation of the sub-intima (28, 37). The synovial layer itself begins to thicken up and form a pannus. This pannus is infiltrated throughout with stiffened scar tissue, which lacks elasticity and recoil leading to further compression trauma in normal joint movement. Neo-angiogenesis follows with new brittle blood vessels and accompanying sensory nerve fibres. This process promotes further inflammation and synovial proliferation ultimately resulting in chronic synovitis (38).

1.4.3 Degenerative haemophilic arthropathy

1.4.3.1 Definition

The effect on cartilage of being in direct contact with blood initiates a break down in the matrix turnover resulting in chondrocyte apoptosis, diminished structural and mechanical ability of the cartilage layer and eventually overall joint integrity. Haemophilic arthropathy is the consequence of repeated joint bleeding and is characterised by chronic synovitis and cartilage destruction, epiphyseal enlargement and bony deformity (39), and has been shown to have predominantly degenerative, rather than inflammatory, characteristics (40).

1.4.3.2 Articular cartilage

Articular cartilage is a highly specialist connective tissue found covering the ends of bone in diarthrodial joints. At only 2-4 mm thick, its primary function is to provide a smooth and lubricated surface for articulation, whilst transmitting loads in weightbearing with low friction. It is a tissue that is avascular, aneural, devoid of lymphatics and with only one cell type – the chondrocyte (41). The chondrocyte is a highly specialised and metabolically active cell with limited potential for replication. It is responsible for the development, maintenance, and repair of the extra-cellular matrix (ECM). The matrix itself is predominantly water (up to 80%) along with collagen, proteoglycan, electrolytes, and other proteins. Each chondrocyte is responsible for maintaining its one micro-environment with the sole purpose of retaining water in the ECM, which is critical for mechanical function (42). Preservation of a homeostatic environment for the ECM and the chondrocyte is essential. However, it is this homeostasis that is severely interrupted with repeated joint haemorrhages in haemophilia.

1.4.3.3 Clinical presentation

People with haemophilia over the age of 65 had no access to regular treatment until they were in adulthood, with those currently aged in their 40's having no access to effective treatment for the majority of their childhood (43). Consequently, many PWH have chronically painful, multi-joint haemophilic arthritis, involving 4-6 of the main joints affected by haemophilia – the elbows, knees, and ankles (9, 44-46). Although yet to be fully elucidated, the reason for these anatomical locations it is likely associated with a combination of synovial vascularity, articular mechanical forces and a shift in the haemostatic balance (28, 47).

1.4.3.4 Pathogenesis

Early investigations into the pathophysiology of the haemophilic joint described widespread haemosiderin loaded synovial cells, cartilage fibrillation, thinning and ultimately full thickness erosions (48). The abnormal synovial lining was characterised by thickened vascular pannus sat atop a highly disrupted sub synovial layer, that displayed few remaining normal synoviocytes but had mass infiltration of thickened scar tissue (49). This now fibrotic and stiff tissue had limited ability to synthesise and secrete glycosaminoglycans necessary for cartilage health. As well as increased collagen deposits, discrete inflammatory infiltrates were also described alongside

these now deep synovial blood vessels and beside subsynovial haemosiderin (iron) deposits (49).

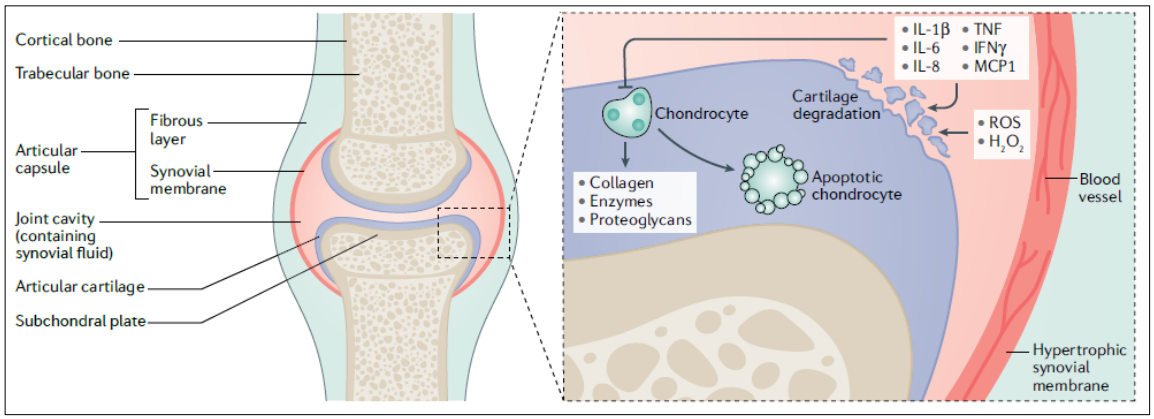


Figure 2: The pathophysiological process of haemophilic arthropathy: the direct effect of bleeding and indirect effect of inflammation on cartilage health (From Berntorp et al 2021) (1)

The thickened synovium projects over the damaged articular surface and grows down into the clefts in the cartilage surface itself, further eroding the cartilage, as well as developing intrasynovial adhesions and capsular fibrosis and diminishing elasticity of both structures (28, 48, 50). Developing granulation tissue in the space adjacent to subchondral bone with the invading vascular synovium initiates local bone resorption. It is this process that is likely to cause the phenomenon of sub chondral cyst development (48).

A pathological imbalance in cartilage and bone turnover in the joints of PWH is highlighted across a spectrum of haemophilic arthropathy damage (51). Early in-vitro studies on articular cartilage exposed to blood found that the turnover of the extracellular matrix accelerated and chondrocytes died off (52), and that this effect likely increased in less mature cartilage (53). The damaging effects of cytokine cascades and hydroxy radicals produced as a result of the blood-induced inflammatory process have also been shown to cause the death of chondrocytes in haemophilic joints (54, 55). Whilst the complex nature of the degenerative process associated with haemophilic arthropathy is not yet fully elucidated, it is accepted that there is likely no minimum number of bleeds required to cause irreversible damage to the overall health of articular cartilage (56).

1.5 Burden of haemophilic arthropathy

Haemophilia is associated with high aggregate costs and imposes a high financial burden on individuals, healthcare systems and society in general. The associated cost to the NHS in treating severe haemophilia has been estimated to be in excess of £228 million per year, with 99% of that cost associated with clotting factor treatment (57). This translates to approximately £110,000 per patient and includes direct and indirect costs to the PWH associated with hospital attendances for bleeding episodes and clinical appointments, as well as the loss in wages and time costs associated (57). Even though the medical treatment comes with a significant cost, the advantages to health and well-being are also considerable. O'Hara and colleagues (2018) conducted a systematic review looking at long term outcomes from either being on prophylaxis or an on-demand treatment. They reported that the median number of joint bleeds for those on episodic (on-demand treatment) was 6 times higher than for those on prophylaxis, and concluded that prophylaxis allowed better joint health, bleed control, quality of life and productivity (in work/society) (27).

Symptoms of haemophilic arthropathy are related to further costs associated with managing haemophilia. The presence of joint arthropathy makes it difficult to distinguish between the sensation of an acute joint bleed and that of arthritic pain (58). Ultrasound examination has demonstrated that some 63% of painful joint episodes in PWH are actually arthritic in nature without bleeding (59), and it is this similarity of symptom sensation that may account for the significant use of high cost clotting factor by PWH to treat their haemophilia related joint pain (60, 61).

The extent of joint damage experienced by PWH is related to the age of the individual and the availability of treatment. A recent UK study of data from the National Haemophilia Database highlighted that those younger PWH (<19 years old) had little or no joint damage due to having treatment since infancy, whereas those over 40 years old had significantly higher levels of joint disease (9). Increasing severity of joint damage alongside the increased number of joints affected in older adults has also been shown to be strongly correlated to poor perception of function in adults with severe haemophilia (46) and moderately correlated with pain (62).

An evaluation of a small cohort of Italian men with haemophilia over the age of 65 found that almost all the participants had widespread multi-joint arthropathy. Whilst most reported being depressed and having issues with bathing, transport and dressing, only 30% reported the presence of chronic pain associated with HA (44). A further study comparing the health status of 102 PWH with age matched normals' found that over 78% of PWH had physical disabilities related to their haemophilia compared to less than 7% of age matched peers (63).

1.6 Pain in haemophilia

Pain as a sign of bleeding and a symptom of long-term musculoskeletal damage secondary to bleeding is a well acknowledged complication of haemophilia. In recent years it has become an aspect of their condition that many PWH feel needs attention. Interventions for acute and chronic pain management was highlighted as a top 10 research priority in a recent James Lind Alliance priority setting partnership that included people living with bleeding disorders and clinicians (64). The recognition from all stakeholders of the ongoing uncertainties in evidence for effective pain management in this population indicates an urgent need for change.

1.6.1 Incidence

Current data indicates that the experience of pain is an unavoidable reality for many PWH, with figures suggesting between 49-61% of PWH experience pain on a daily basis (65, 66). Episodic acute pain is reported in 20-68% of adults (60, 66) with chronic pain experienced by 30-71% of adults (66, 67) and in 19% of children (68). One study evaluating children and adults with haemophilia in Portugal found that 88% of their cohort reported a lifetime of pain that they associated with having haemophilia (69). There remains a lack of standardisation in collecting information relating to pain in PWH, associated with widely heterogenous cohorts, varying definitions of pain and the socioeconomic factors of access to adequate healthcare. Whilst the elbow and knee continue to be affected by painful haemophilic arthropathy, an increasing number of studies are reporting the ankle to be the most painful affected joint in both adult and paediatric cohorts (66, 69-71).

1.7 Pathophysiology of pain

Whilst pain has long been recognised and reported as a symptom in PWH, little has been published describing the potential mechanisms at play in the acute or chronic pain experience for PWH. Acute and chronic pain have been more attributed to temporality of a bleeding event or the assumed association in the presence of haemophilic arthropathy, as opposed to consideration within a model of pain neurophysiology. Understanding the potential mediators of the pain experience is important in being able to reason and conceptualise what intervention(s) may be helpful to PWH. This section will present what is currently understood about the neurophysiological basis of the pain experience in haemophilia.

1.7.1 Nociception

Nociception is the object of sensory physiology and is defined as the neural process of encoding and processing noxious stimuli (72). Whilst pain has classically been viewed through the narrow lens of nociceptive processing, nociceptive neurons, pathways and peptides may or may not give rise to pain perception or pain behaviour (73). The experience of pain itself reflects an interaction between memory, attentional and affective brain circuitry and afferent sensory inputs and therefore is uniquely representative of, and to, the individual experiencing it (74).

Nociceptors are small and medium-diameter cell-based bodies, including unmyelinated, slowly conducting C-fibres and thinly myelinated, more rapidly conducting Aδ fibres. Both types are distinguished by their responses to noxious thermal and mechanical stimuli and tissue injury (75) and are present in the bone, ligaments, capsule and synovium of human joints (76, 77). Perceptual awareness and the experience of acute pain is the result of a threshold phenomenon, whereby an increased responsiveness and sensitivity of nociceptors in response to potentially dangerous noxious stimuli is transformed to a conscious event (73). The resultant behavioural response is focussed on minimising injury and to protect the organism from further injury and promote healing (74).

The acute pain experienced from joint bleeding events in PWH is likely evoked by a complex combination of nociceptor stimulation from the rapidly expanding joint capsule, secondary inflammation from the damaged bleeding blood vessel and the

biochemical response from the overwhelmed synovium (28, 78). The behavioural response in PWH is then associated with infusing factor concentrate (if available) and resting the affected joint. These processes may be enhanced further if the joint in question also has underlying chronic haemophilic arthropathic changes such as chronic synovitis, thickened joint capsule and cystic bone changes.

Although yet to be fully elucidated, it is likely that chronic joint pain in PWH is similar to the processes observed in OA and RA, and involves a process of chronic nociception (79). Neovascularisation has been noted in advancing OA to be a probable nociceptive promoter, likely irritating sensitised C-fibres in thickened capsule structure by the production of pro-inflammatory cytokines (80, 81) and is likely this process adds to the joint pain reported by some PWH (82). Chronic nociception has recently been acknowledged as a condition in its own right by the International Association for the Study of Pain and is a classification of chronic pain by the anatomical changes seen in the joints (83). Pathologic changes to the synovium and capsule as well as the pro-inflammatory processes and cellular interactions likely contribute to persistent joint pain in PWH through both peripheral and central mechanisms (84, 85).

1.7.2 Nociplastic pain

Nociplastic pain is distinct from that of nociception, in that pain is experienced in the absence of clear tissue involvement for nociceptive input and may be more widespread than just one pain site. It is attributed to altered pain modulation and sensory processing and its identification is important as it does not respond to interventions aimed at nociception (86). Quantitative sensory testing is a method to evaluate aspects of pain hypersensitivity associated with nociplastic pain and include assessments of algometer induced pressure pain thresholds and temperature (87). Some recent small studies have sought to evaluate the presence of nociplastic pain states in PWH with haemophilic arthropathy. Comparison of pressure pain thresholds in PWH against normals has shown PWH to have decreased pain thresholds at their affected joint as well as other bodily locations not affected by arthropathy (88-90), indicating the presence of altered nociceptive processing. As yet the clinical relevance of these data remains to be elucidated, although they do indicate the potentially complex neurophysiological mechanisms that are involved in the pain experience of PWH.

1.7.3 Pain as a multifactorial experience

Viewing pain as a purely neurophysiological phenomena is reductive and risks ignoring or invalidating the experiences of the person reporting it. Current science now conceptualises pain not as a static experience, but as a perceptual continuum that emerges from the co-ordinated activity of multiple aspects of an integrated central nervous system (91, 92). Importantly, chronic pain is acknowledged not just as a symptom of injury or illness but as a disease entity in its own right (83, 93). The recently updated definition of pain from the International Association for the Study of Pain recognises the developments in understanding of pain science in defining pain as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage' (94).

There are multiple, complex components involved in how pain is experienced, and they are not the same for any one individual. Pain as a perceptual output is a dynamic interplay and integration of elementary sensations, with motor, sympathetic, immune and neuro-endocrine system activity, and complex functions related to memory, affectivity and emotion (95). Humans are embodied and action oriented and as such, seek to make sense of pain (96). This sense making process involves not only the internal bodily environment, but includes scrutiny of the outside environment, as well as recall and sampling of relevant past experiences (97). A judgement is then formulated on the meaning of a particular pain experience, from which expectations of consequence then develop (98).

The complex, multi-dimensionality of the pain experience therefore demands a person-centred approach to management and support for those people living with pain. The Faculty of Pain Medicine of the Royal College of Anaesthetists recommends that pain management programmes be delivered in a biopsychosocial model by knowledgeable, specialist multi-disciplinary teams (99). This provides a lens that recognises the complex multidimensional nature of pain and addresses it in the context of cognitive, affective, behavioural and social characteristics (93). This approach when appropriately used in the management of chronic pain in arthritic conditions creates a patient-centred framework, whereby intervention is guided by the assessment of patient needs, beliefs, preferences, priorities and goals (100, 101).

1.8 Relationship between pain and haemophilic arthropathy

The proposition of a direct association between pain and the presence or degree of haemophilic arthropathy remains a biomedical lens through which much of the issue of pain is considered in PWH (102-104). However, it is clear from the literature that such a view is misconceived, even allowing for the large variance in how the presence of pain is assessed. Multiple studies clearly describe both a subjective and objective mismatch between joint damage and pain. The large, multi-national, Haemophilia, Experiences, Results and Opportunities (HERO) online survey study reported results from 675 adults with an average age of 36 (18-86) (105). Amongst the diverse amount of person relevant data collected, participants were able to subjectively report the presence of joint disease as well as completing the EQ5D-5L questionnaire. Whilst 35% reported pain (via EQ5D5L) in the presence of haemophilic arthropathy, 34% reported pain without the presence of arthropathy. Similar differences were reported in a questionnaire survey of young adults in the USA where 44% of 25-34 year olds self-reported living with arthropathy but only 16% of them reported pain as measured by a Five-point scale (106). A survey of adults with haemophilia in Ireland taking part in the iPATH study, found that whilst all of the 47 participants had arthropathy, only 71% had pain as measured by the Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire and 58% reported functional difficulties (107). A large survey of haematologists in 23 haemophilia centres in Europe reported on the datasets for 2224 adults. Their analysis found that 70% of those individuals were living with haemophilic arthropathy, but only 38% were reported to have chronic pain (68). However, precision and patient value in this study data must be questioned due to the third hand reporting of PWH clinical data into the questionnaire.

More objective approaches evaluating the relationship between the presence of joint damage and pain add similar findings to the subjective reports detailed above. A recent study investigated the relationship between ankle pain, structure and function in 30 people (60 ankles) with moderate or severe haemophilia (108). Pain intensity and interference was evaluated using the brief pain inventory and pain sensitivity was evaluated using pressure pain threshold algometry. Joint structure was assessed with ultrasound and MRI. Whilst 83% of the participants had more than one painful joint and 76% and 55% of them had abnormalities on MRI for their talocrural and subtalar

joints respectively, analysis found no correlation between pain intensity/sensitivity and joint damage. This finding is similar to Van Genderen and colleagues (2006) who reported no association between pain (as assessed using the McGill questionnaire) and arthropathic findings on X-ray (45). Lack of correlation between VAS pain scores and assessment of joint health using the HJHS was also found in a study by Ucero-Lozano et al (2022) (109). They did however note that the presence of pain correlated to mental health indicators of quality of life. Others have noted similar correlations between pain and employment status (105, 110) as well as the presence of anxiety/depression and the use of opiates (110).

1.9 Pain assessment in haemophilia

There is no standardised or accepted method of assessing pain in PWH. The recently updated treatment guidelines from the World Federation of Haemophilia recommend only 'age appropriate assessment tools' (111). Such an open recommendation seems to presume clinicians have sufficient knowledge and skills to choose an appropriate assessment tool, which may account for the lack of standardised approach to assessment observed in the literature.

A wide variety of approaches to pain assessment are used in PWH. The haemophilia joint health score was developed as a standardised tool for assessing joint health in children. As well as assessing swelling, muscle strength and range of movement at the elbow, knee and ankle, it also includes the assessment of pain in non-weightbearing active joint movement or on palpation (112). This highly reductive assessment takes no account of pain with functional activity or its relationship with the person as a whole. In contrast, the PROBE questionnaire includes questions about pain in an acute and chronic state, and pain interference in activities of daily living (113). With this degree and type of detail it has, at population level, been able to highlight the impact of acute, chronic and acute on chronic pain on quality of life in PWH (114). However, the PROBE questionnaire is yet to be evaluated for use in day-to-day practice or as a method of evaluating change after a discrete intervention.

In recent years, studies have used the VAS as the only pain assessment, regardless of the number of painful joints or temporal nature of the pain being assessed (45, 65, 115). Others have reported pain based on the EQ-5D-5L/3L questionnaires (110, 116),

or had a binary question of the presence (or not) of pain and whether it was acute or chronic (60, 106, 117). A Canadian team have worked with PWH in co-developing a clinical assessment tool that aims to enable better clinical communication about pain (118). Although currently only tested in small number of people to date, it may hold promise in facilitating improved clinical management.

1.10 Burden of pain associated with haemophilic arthropathy

Significant limitations imposed on life by both haemophilic arthropathy and pain are described by PWH. Living with chronic pain brings with it constraints in mobility and independence, increased anxiety, poor quality of life, and frustration due to restrictions in activities of daily living (119, 120). A qualitative study of 14 adults with haemophilia found that many had experienced limitations whilst at school, and expected that living with pain was a part of their life with haemophilia. They voiced frustration at being unable to participate in activities with friends or family as well as the loss of physical activity opportunities when young due to fear of bleeding and overprotective parents (121). A Europe-wide study of PWH in five countries described a significant economic burden for individuals with haemophilic arthropathy, mostly related to transport to, and frequency of, hospital visits, medication costs and surgery. This cost was reinforced by the psychosocial impact of pain and disability related to their arthropathy that limited their employment opportunities (122). Haemophilic arthropathy, particularly in the joint of the lower limbs, brings anxiety with being active and also accentuates fear of falling. (123).

It is noteworthy that the concerns for many PWH in these studies are multifactorial and focus heavily on their abilities to participate in activities that they want to do. The range of behaviours affected, altered, and limited by pain and arthropathy highlights the need for a whole person focus on potential interventions to ameliorate the issues at hand. However, most recommendations for clinical management, including those from the World Federation of Haemophilia (WFH), relate only to pharmacological management of pain(111, 124, 125), thereby substantiating the basis of why PWH have identified pain management as a key research area for them (64).

1.11 Management of haemophilic arthropathy and pain

Consensus on best practice management for acute pain episodes in PWH revolves around bleed management. Administration of clotting factor concentrate in an acute bleed event is considered an acute pain management intervention. It may also require concomitant pain medications and other adjunctive measures, such as behaviourally mediated activities that include ice application, rest and splinting (111). Chronic pain presents additional challenges, likely due to multifactorial influences that include ineffective assessment, lack of knowledge of pain mediating factors and a lack of evidence-based interventions.

It remains unclear what matters and what works for individuals when considering effectiveness of pain management. Figures vary from 21-50% of PWH reporting that they did not believe their pain was well managed (66, 69). Low perceived success of pain management may in part be reflective of a lack of standardised local pain management pathways for PWH. Whilst the haematologist is the usually approached first in relation to pain (69, 126, 127), others such as the GP and orthopaedist/orthopaedic surgeon are used (115, 128), with some using specialist pain clinics (115, 129). Few authors discuss in detail how pathways may vary, if at all, for acute and chronic pain presentations, thereby making recommendations difficult.

1.12 Pain management approaches

1.12.1 Pharmacological pain management

Whilst not actually being a pain medication, clotting factor concentrate (CFC) is the most commonly and frequently used approach to treatment of pain in PWH. Between 79-100% of PWH report using CFC to treat acute pain. This figure drops only very slightly to between 38-81% in chronic pain (61, 126), but no study to date has evaluated the efficacy or cost effectiveness of this strategy.

Despite being the primary recommendation for pain management in current guidelines, there remains limited high quality studies evaluating effectiveness of pain medications in PWH. It is estimated that 35-51% of PWH take acetaminophen and/or non-steroidal anti-inflammatory drugs (NSAID's) for pain (60, 126). A more recent study indicated that 56% of adults and 21% of paediatric PWH had been exposed to opioid based medications, although the authors indicated that the true figure for those

on opioids was probably higher than those published (130). Whilst the safety of using acetaminophen in PWH has long been established (131), concerns of potential toxicity do remain for those living with co-existing HIV and HCV (132). Use of NSAID's are generally not recommended for PWH due to the potential bleeding associated with their anti-platelet effect (133). However, cyclooxygenase-2 selective NSAID's, such as Celecoxib and Eterocoxib which have minimal platelet interaction, can be used safely with appropriate monitoring (134-136).

1.12.2 Self-reported pain management

The apparent incoherence in biomedical pathways may help contextualise the wide range of non-pharmacological strategies used by PWH that are reported in the literature. The use of factor concentrate is widespread in cases of acute and chronic pain (60, 115). The RICE (rest, ice, compression, elevation) regime, or components thereof, remains one of the most frequent non-pharmacological approaches used by PWH for both acute and chronic pain episodes (60, 137, 138). Other reported strategies for chronic pain include prayer/faith, swimming, relaxation and deep breathing techniques, acupuncture, diversional activities, and exercise (61, 66, 115). Effectiveness is difficult to elucidate due to high heterogeneity of reporting cohorts and poor/minimal detail on the dosage and use of the interventions themselves.

1.12.3 Psychological and complimentary therapy

The current evidence for use of psychological based therapies for pain management in PWH is limited. A small study investigating the use of hypnosis for pain management in adults with haemophilia found no significant improvement in pain interference (139). One UK-based study investigated the effect of an educational DVD on motivation to self-manage pain in PWH. Results demonstrated a shift from the pre-contemplative to contemplative stage of thinking about readiness to change. The authors suggested a potential benefit in preparing PWH for participation in more intensive pain self-management (140). A more recent controlled study sought to evaluate an intervention combining cognitive behavioural therapy (CBT) and exercise-based intervention in 19 PWH. Significant improvements in pain intensity and quality of life were reported, although it is difficult to ascertain the effect of CBT alone as the control group carried on with usual activities as opposed to using only the exercise component that had been combined with the CBT (141).

A few studies have evaluated the effects of complementary therapies such as acupuncture on arthritic joint pain in PWH. A single case study report for chronic elbow and knee haemarthropathy pain highlighted that as well as pain reduction for up to 14 months, the patient also reduced their pain medication usage (142). Further studies using highly variable needle positioning over multiple sessions showed similar results with pain reduction measured by VAS (143) and accompanying improvement in reported quality of life (144, 145). Whilst the use of acupuncture appears safe with respect to bleed risk, the paucity of data means further research is needed to fully evaluate any potential benefit for pain.

1.13 Physiotherapy and pain management

Interestingly, whilst physiotherapy is consistently extolled as an important and key component of overall haemophilia care, physiotherapy (as an option in pain management) is discrepant, reportedly used by between 12-46% of people (115, 128). However, what that physiotherapy may entail and in what context (acute or chronic pain) is poorly described, as is the effectiveness of such physiotherapy intervention. Understanding the historical perspective of physiotherapy provision in haemophilia care may provide some indication for this finding and highlight the gaps in clinical care and research priorities.

1.13.1 Historical context for physiotherapy in haemophilia

Even with the significant musculoskeletal effects of haemophilia, physiotherapy as a regular component of care has existed for a relatively short period of time. The development of treatment options for bleeding, in turn enabled the creation of healthcare teams with specialist knowledge and understanding of haemophilia, and so it was that active therapeutic intervention with physiotherapy became a reality for PWH in the early 1960's. The traditional modalities of ice, immobilisation splints and lower limb traction were accompanied by electrotherapeutic modalities such as Galvanism for muscle stimulation, and ultrasonic iontophoresis with hyaluronidase (theorised to speed up absorption of extravasated blood in the tissues) (146-148). The focus of intervention was enabling the recovery of a joint or muscle back to a pre-bleed state of normalised range of movement, strength, and flexibility. Even with very limited published clinical management advice, the basis of the message was one of acute bleed management framed within a concept of resolution of joint health.

The discovery of cryoprecipitate and its use in home treatment by PWH, and it's positive effect on life expectancy and quality of life (149) enabled further development of physiotherapy interventions for PWH. Interventions shifted from being carefully timed and planned, to having physiotherapy initiated less than 24 hours after bleed onset to regain full mobility and activity, in an approach that pushed for healthy activity especially exercise (in children) (150). Therein developed a clinical management plan that limited splinting to 24 hours (as long as they had received treatment) and the instigation of range of movement and isometric muscle activity as soon as possible (151). Pain however, presented 'considerable therapeutic difficulty' (151) and whilst advanced haemophilic arthropathy management was viewed as a 'palliative' endeavour, there was still a view that it was possible to maintain adequate function required for living, if given enough factor concentrate to facilitate vigorous activities (152).

1.13.2 Haemophilia treatment advances and physiotherapy

It is notable that the hope for improvements in joint health seen with the developments in bleed/haemostasis treatment is not reflected in an increase in studies evaluating physiotherapy. With the scientific advances of genetic cloning of FVIII and the subsequent development of recombinant factor concentrate in the late 1980's, the 1990's witnessed the mass production of extremely safe clotting factor concentrates and a significant change to bleeding patterns seen in PWH as a result. However, the push forward in medical science seen in the clinical treatment of haemophilia remained unmatched in respect of physiotherapeutic management of the musculoskeletal co-morbidities of haemophilia. This dearth of research was noted to be a result of the catastrophe of viral-co-infections diverting attention away from musculoskeletal problems (153).

1.13.3 Physiotherapy as a biomedical paradigm

Best practice papers and opinion pieces dominated the literature for almost two decades, often with a predominantly paediatric focus. Recommended interventions ranged from general advice for management of chronic synovitis (154), conservative management of joint bleeds (155), the use of ankle/knee joint orthotic devices (156, 157), ankle proprioception training (158), and rehabilitating muscle imbalance (159). What all these opinion pieces had in common however was a unimodal, biomedically

orientated paradigm towards musculoskeletal rehabilitation. Joint health was viewed independently of evolving longer-term damage and focus was on resolution of bleeding and restoration of a joint or muscle to a normal state (as defined by a textbook concept of normality, strength, range of movement or flexibility).

It is worth noting that the modern concept of evidence-based practice in healthcare was developing at pace in the mid-late 1990's (160, 161). Whilst there was an increasingly solid evidence-base for managing and preventing bleeding in PWH, there was a growing mismatch with allied research relating to rehabilitation and musculoskeletal health and well-being. The ongoing biomedical focus of physiotherapy interventions for resolution to 'normal' in the acute phase and minimally described effective intervention for adults with chronic joint disease, highlight a void in haemophilia physiotherapy care at this time. There remains at the end of the 1990's an incoherent and lacking evidence base for physiotherapy approaches for PWH. The focus on the younger PWH and the post-acute bleed management phase means little has been investigated regarding chronic joint issues or older adults with haemophilia. Chronic joint pain is viewed as a biomedical, structurally mediated entity, that is managed via joint mobilisation techniques alongside muscle stretching and strengthening and functional training.

Whilst the benefit of prophylaxis was clear to see, it was not until 2010 that the UKHCDO advised the use of regular treatment for adults with severe haemophilia (162) although such an approach remained controversial for a few years after (163). Expansion in treatment availability marked a seismic shift in both quality and efficacy of treatment available. The result of less bleeding episodes shifted the view of physiotherapy and rehabilitation to an even more biomedical approach, with a focus on promotion of physical normality which is reflected in the research approaches in the 2000's onwards. A focus on acute bleed management with early rehabilitation back to physical normality remains at the fore, with return to baseline a key metric. However, improvements in treatment positions physiotherapy as an enabler of a normal life for children with haemophilia. Increased physical activity is framed around sports participation in well treated populations (164), against a backdrop of damage limitation for children in low/middle income nations with little or no access to any treatment (165, 166). Whilst some do discuss person focussed holistic functional

recovery (167, 168), little advice or information is related to those living with chronic pain secondary to widespread arthropathy. An acute bleeding episode remains the main gateway for access to biomedically oriented physiotherapy.

1.13.4 Current physiotherapy practice approach

The advances in treatment efficacy has seen a shift in the research focus in haemophilia, notably towards paediatric health. In considering the content of much of the physiotherapy literature over the past 30-40 years, management of chronic arthropathy within a conceptualised rehabilitation model does not exist outside of association with an acute bleed episode. The modern evolving clinical issue with chronic pain may well be due in part to the lack of attention given to it over these past years.

The limited historical precedent in the literature informing practice for physical well-being and positive health outcomes serves to widen the gulf between those younger PWH on primary prophylaxis compared to older PWH on tertiary prophylaxis. This view would appear to be confirmed in a recent paper from Canada (169) where a team developed evidenced based practice guidelines for physiotherapy in inherited bleeding disorders. Whilst the recommendation was that physiotherapists should assess pain, the current evidence in practice for this was weak. When considered alongside the strong recommendations for manual therapy and exercise (as a physical health measure) and the recommendations for electrotherapy and acupuncture within conceptual/ theoretical principles, it highlights a research focus on mechanistic physiotherapy interventions rather than multi-dimensional person relevant activities (such as pain). There is developing consensus on the importance of physiotherapy in helping to manage chronic pain associated with arthropathy (170). However, recommendations such as electrotherapy, strengthening, stretching and joint mobilisation continue to focus on interventions done to, rather than with, a PWH (171).

As it stands, many current interventions for both acute bleeding and post-bleed rehabilitation remain based in expert opinion. The enduring unimodal, mechanistic, biomedical approach lacks clarity on what physiotherapy may be able to offer in

helping to moderate and influence the physical, social, and psychological complexities of living with chronic arthropathy and pain.

1.14 Remote delivery of physiotherapy – the case for a telerehabilitation approach

As previously described in the preface to this thesis, the emergence of the Covid-19 global pandemic prompted the rapid development and implementation of technological alternatives for access to, and delivery of, healthcare services remotely. Whilst the use of technology in the context of health provision is not novel, its rapid acceptance into almost every healthcare setting has demonstrated the potential value longer term, as well highlighting limitations with respect to digital access, health worker training, health policy and day to practice (172).

The World Health Organisation assigns the umbrella term 'Digital Health' to cover the application of digital technologies in the context of health (173). Within this broad definition other related terminology exists such as 'Electronic Health', 'Telehealth' and 'Telerehabilitation'. NHS England views digital health as part of 'Technology Enabled Care Services', describing it is as a complex intervention involving people, process and technology, with success dependent on all three elements (174). The relationships between these definitions are described and presented in Figure 3.

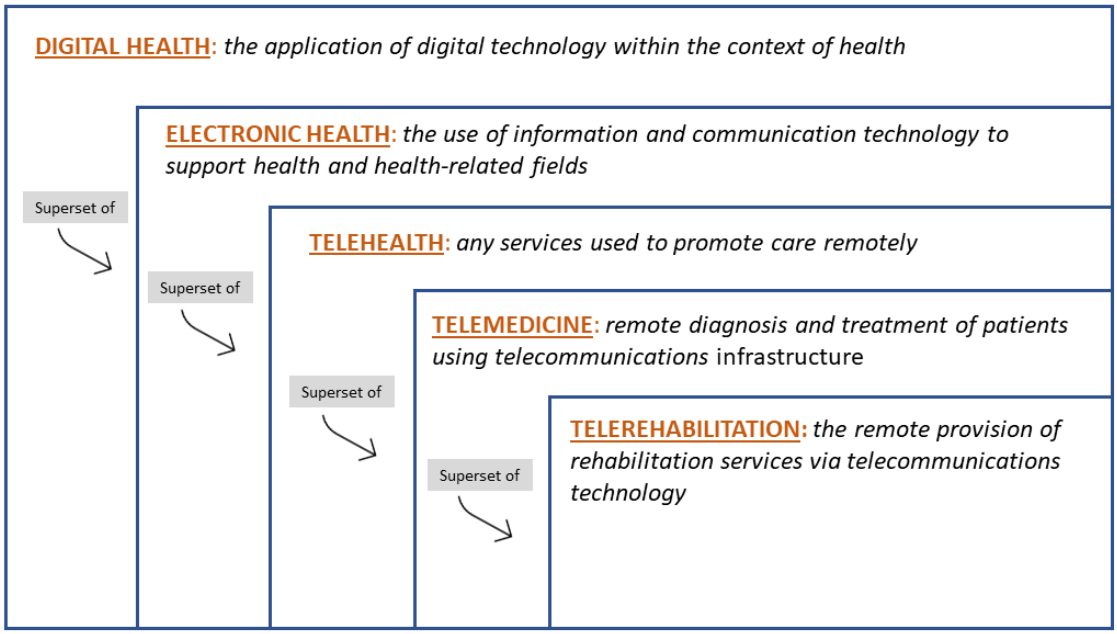


Figure 3: Definitions associated with digital health (adapted from Herold et al 2022)(175)

Telerehabilitation has been defined as the delivery of rehabilitation services using information and communication technologies, and includes the spectrum of rehabilitation input from assessment through to intervention, monitoring and counselling (176). The term applies to a wide range of technology (telephone, tablet, laptop/computer, video-conferencing, internet, augmented and virtual reality, wearable devices and gamified features) and delivery approaches (synchronous/ asynchronous/ combination of both).

Rehabilitation utilising a range telerehabilitation technology and approaches have been described across a spectrum of conditions including neurological impairment (177-179), chronic pain (180, 181), low back pain (182), and a range of chronic musculoskeletal conditions (179, 183). Whilst the cohorts included in studies are heterogenous, there appears to be a general agreement that the provision of rehabilitation via telerehabilitation approach is safe, and in most cases show outcomes comparable to in-person provision.

There have been many proposed positive opportunities associated with telerehabilitation. Time saved and less burden from travel by patients to rehabilitation facilities, as well as equitable access to care due to geographical and socioeconomic barriers are significant moderators of successful participation in telerehabilitation programmes (177, 184). Others urge caution due to limited digital literacy or potential added costs of technology or devices that patients may need to have to successfully take part in telerehabilitation, thereby further emphasizing potential inequity of care (180, 185). Successful integration of telerehabilitation as a standard of care has the potential to improve the patient experience and deliver better value for money (186), and it is imperative that future research helps establish safety, security, accessibility and acceptability of programmes for each patient group.

1.15 Rationale for this thesis

I have been qualified as a physiotherapist for 22 years and worked in the field of haemophilia for 16 years. In my clinical role I have seen first-hand the challenges PWH have with painful acute haemarthroses and that associated with chronic haemophilic arthropathy. The individual functional issues I observed were a result of their unique combination of joints affected with arthropathy, their age and their own experiences of managing their pain day to day. I noticed that for some, a fear of bleeding, anxiety of moving with pain, and a lack of belief in their own potential ability contended with clinical recommendations to move more and participate in exercise and rehabilitation strategies. However, spending time in one-to-one sessions and working together through activities that could be done, helped demonstrate that such an approach could have benefit for them and their pain, and be enjoyable. Further conversations with the PWH I worked with strengthened my desire to undertake this programme of study and helped clarify what kind of approach would be worth investigating. There was a strong emphasis on being able to live better and to be able to do more with the body they had.

There are no published evidenced-based guidelines for management of chronic arthritic joint pain in PWH. Whilst effectiveness of rehabilitation for primary management of pain in osteoarthritis and rheumatoid arthritis is well established (187-189), there has been no structured scientific research to evaluate the effect of a rehabilitation programme for management of chronic pain in PWH. To date no studies have established what aspects of a rehabilitation approach may be effective for pain management in PWH, or what PWH would be able to, or find acceptable to, participate in.

PWH want knowledge about their condition to allow them to develop tools and decisions about treatment, exercise and activity (190). However, knowledge of the potential benefits of rehabilitation as a management strategy for chronic joint pain appears limited. The lack of guideline for chronic pain management in PWH means the knowledge, confidence and pathways used by haemophilia clinicians such as haematologists, specialist nurses and physiotherapists, in managing chronic joint pain, is unclear.

1.16 Aims and objectives for thesis

1.16.1 Overall Aim

The primary aim of this thesis was to develop and test the feasibility of an exercise-based telerehabilitation intervention for people with severe haemophilia and chronic pain associated with haemophilic arthritis. This study will be referred to as the REMAP-Haemophilia study throughout the thesis. (**RE**habilitation for the **M**anagement of **A**rthritic **P**ain in **Haemophilia**)

1.16.2 Objectives

The thesis followed the stages described in the Medical Research Council framework for developing complex interventions. The objectives of the study were:

MRC Framework stage: Development and modelling

1. Define the evidence for the effectiveness of existing physiotherapy interventions for pain management in PWH
    a. Overview of the current literature
    b. Systematic review evaluating outcomes of pain, function, and quality of life of physiotherapy interventions for pain management
2. Explore and understand the views and experiences of PWH and clinicians on
    a. Living with pain and haemophilia
    b. Pain management approaches
    c. Beliefs and expectations on using exercise as a potential pain management approach
3. Develop and define a stakeholder informed programme theory that will underpin the study protocol for a telerehabilitation exercise intervention (REMAP-Haemophilia)

MRC Framework stage: Feasibility testing

4. To test the feasibility, acceptability, and safety of the REMAP-Haemophilia intervention

The thesis structure and methodology used are described in detail in Chapter 2.

Chapter 2 - Methodology

This chapter presents the methodological approach taken in the thesis. The epistemological and ontological position are described and how it relates to the decision to choose a mixed-methods approach. The concept of developing a complex intervention and using the Medical Research Councils framework to inform and underpin the development of the body of work will be described. The importance of stakeholder involvement in intervention development will discussed, and where this has been integrated in this thesis will be presented. The philosophical considerations of positivism, interpretivism, pragmatism and critical realism will be introduced with discussion on how they were considered in relation to the methodological choices made.

2.1 Intervention development

Intervention development has been defined as the description of the rationale, decision making processes, methods and findings which occur between the inception idea of an intervention until it is ready for a formal feasibility, pilot or efficacy testing (191). The space between the actual intervention and the expected outcome is often referred to as the 'black box' (192), and it is becoming increasingly important to both funders of research as well as developers. The black box is conceptualised as something that can provide a better understanding of 'how' and 'why' an intervention may be having its observed effect. Importantly, the black box incorporates assumptions about the people, behaviours, context and culture that exist as an intervention is implemented (192, 193).

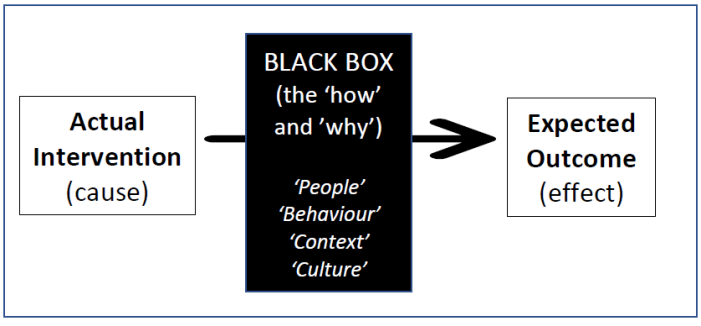


Figure 4: Illustration of the 'black box' of complex interventions

A persistent focus on effectiveness as the primary outcome can create the phenomenon of research waste on studies that do not show effectiveness. This is attributed to poor question selection, inadequate reporting, and poor intervention description (194). The process of intervention development itself should be dynamic, creative, open to change and forward looking to future evaluation and implementation (195).

2.2 Defining a complex intervention

An intervention is considered complex due to the properties of the intervention itself. These include the number of components involved, the range of behaviours being targeted, the expertise and skills required by those delivering or receiving the intervention, the number of groups or settings targeted and the permitted level of flexibility of the intervention or its components (196). The UK Medical Research Council (MRC) first published its guidance framework on the development and evaluation of complex interventions in 2000 (197), which was further expanded in 2006 (198). The framework highlighted a four-stage process of i). Development, ii). Feasibility/piloting, iii). Evaluation and iv). Implementation. In the 2006 edition there was an attempt to provide a less linear process model, with bi-directional arrows between phases used to highlight a more recursive and iterative approach (Figure 5).

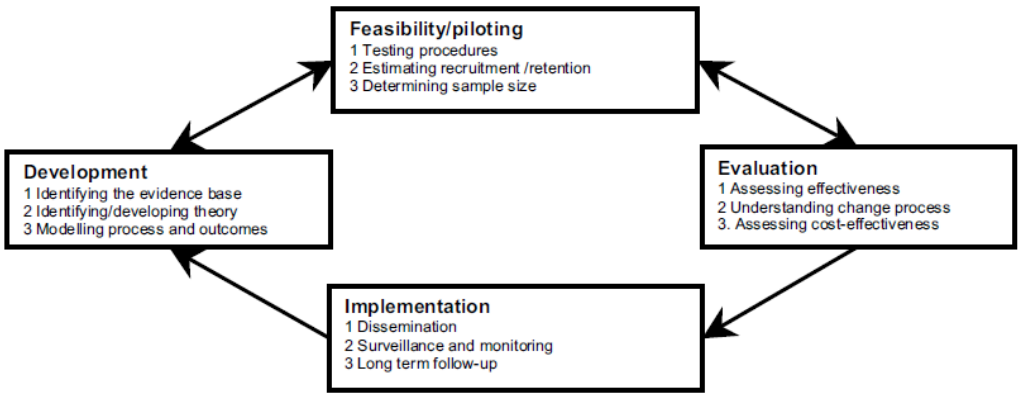


Figure 5:The 2006 MRC framework for developing complex interventions

Whilst there was some basic explication of the requirements of the development phase including evidence base identification, developing theory (with stakeholders), and modelling the process, this 2006 model has been criticised due to the lack of detail

allocated to the 'how' and 'why' of the development process itself. However, the authors did acknowledge at the time a lack of consensus on best practice for such activities (198). In the years following the publication others provided more detailed guidance around the development phase specifically. There was particular emphasis on the importance of contextual effects and influence in any trial activity and delivery, and theory development to underpin the intervention for delivery and for future evaluation. Bleijenberg and colleagues (194) proposed incorporating the needs of both the providers and recipients of the intervention so that perceptions, preferences and capacities of both are taken into account to improve external validity value. Others highlighted the value of stakeholders in identifying priorities that matter to them, solutions that may make a difference to future real world implementation and co-producing content, style, format and delivery aspects of an intervention (195).

The most recent updated MRC framework (Figure 6) acknowledges this and has sought to focus attention on understanding how, and under what circumstances, a intervention may bring about change (196).

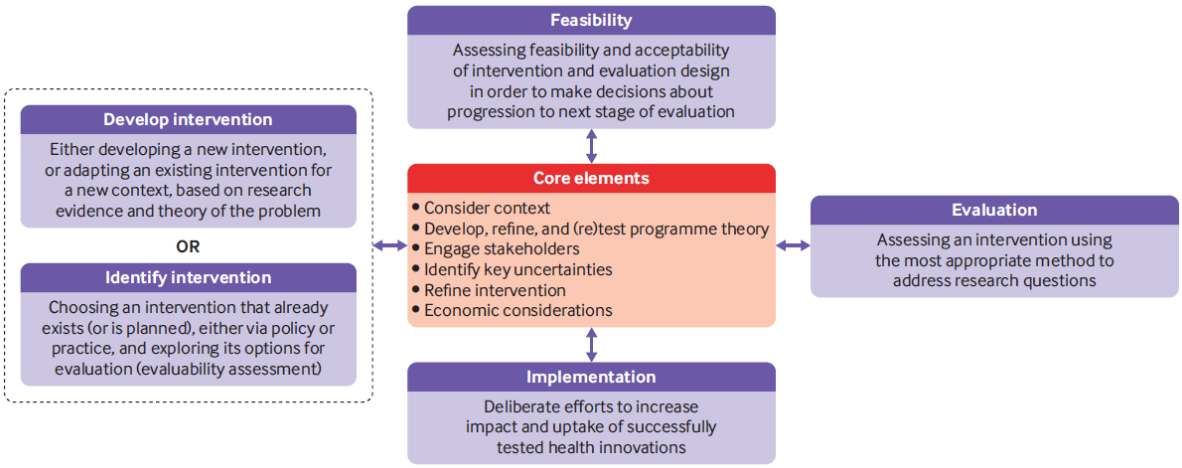


Figure 6:The updated 2021 MRC framework for developing complex interventions

This new framework identifies four perspectives of efficacy, effectiveness, theory based and systems thinking in a pluralistic approach to intervention development. More importantly it now places context, theory development and stakeholder engagement as core elements related to all phases not just the development phase.

The MRC framework was chosen for this thesis as it provides a coherent approach that is well recognised by other healthcare researchers. The staged approach to the guidance helps to create a logical and transparent method to intervention development. Table 2 details how this thesis reflects the stages of the framework.

Table 2: Thesis components aligned to the MRC Framework

MRC Framework Phase	MRC Component	How this thesis addresses this	Chapter
Developing intervention	Identify and review the published evidence base	- Review of the literature around pain incidence, its burden, and the current medical approaches to its management in haemophilia - Systematic review of physiotherapy interventions and their effect on pain	-Chapter 1 -Chapter 3
	Develop theory	- Review of the existing literature - Undertake qualitative inquiry to better understand the lived experience - Review behavioural change theories and how they may be incorporated - Stakeholder participation in theory development	-Chapters 1, 3 -Chapter 4 -Chapter 5 -Chapter 5
	Articulate Programme theory	- Creation of a visual programme theory map and written report of the process and detail of the causal model	-Chapter 5
	Modelling process and outcomes	- Identify appropriate methodology and methods to address the research aims - Explicate the reason for choosing approach and outcome measures used in the study protocol.	-Chapter 2 -Chapters 5, 6
Feasibility	Evaluating feasibility and acceptability of intervention	- Assessed via quantitative and qualitative methods	-Chapter 7
	Evaluating recruitment, retention, and adherence to study	- Assessed via quantitative and qualitative methods	-Chapter 7
	Evaluating Safety	- Assessed for adverse events and bleeding	-Chapter 7

2.3 Mixed methods research

Mixed methods research can be viewed as an intuitive way of doing research that is constantly being displayed throughout our everyday lives, as it mirrors how we 'collect' evidence that helps us make sense of the world (199). It is an approach to knowledge that considers multiple viewpoints, perspectives and positions whilst acknowledging the strengths and respecting the wisdoms of both quantitative and qualitative views (200). Based on the intent rather than the priority of a study, it has been defined as a way of rigorously collecting, analysing and integrating quantitative and qualitative data, whilst organising these procedures into specific research designs that provide the logic and procedures for conducting the study, and all framed within theory and philosophy (199). It is this focus on the method and design assemblages, rather than just the act of mixing, that must make sense for answering significant research questions (201).

The integration of quantitative and qualitative data uniquely defines mixed methods research and puts it apart from multi methods research - where a series of complementary methodologies are used in parallel or sequence but are not integrated until inferences are being made (202). The choice of a mixed methods approach for the current study approach over a multi method approach allows a depth of qualitative understanding with the reach of quantitative techniques, providing a dense, analytic picture of wider and deeper, rather than just reliable and valid, findings (203).

2.3.1 Study design

Deciding if the design of the mixed methods study is going to be fixed (use of qualitative and quantitative methods predetermined from the start) or emergent (use of mixed methods arise due to issues that develop) is an important step to determine which core design to use (199). Three core mixed methods designs are advocated (Figure 7) and differ in regards to the focus of data collection and point of interface between the quantitative and qualitative data (199, 204). In a convergent design, the conceptually separate quantitative and qualitative data are collected and analysed separately using their appropriate methods. The datasets are then integrated and interpreted according to the aims of the study. The intent with this approach is to gain

different but complementary data on the same topic. The explanatory sequential design sees initial quantitative data being collected and analysed, followed by qualitative data collection and analysis which is then used to help explain the quantitative findings. This design approach is best suited to studies where the quantitative data may be difficult to interpret or appear incomplete. The most complex approach is that of an exploratory sequential design where the analysis of initial qualitative informs the creation of a quantitative tool or intervention which is tested in a follow up study. This design is best suited for exploring a phenomenon where little previous data exists.

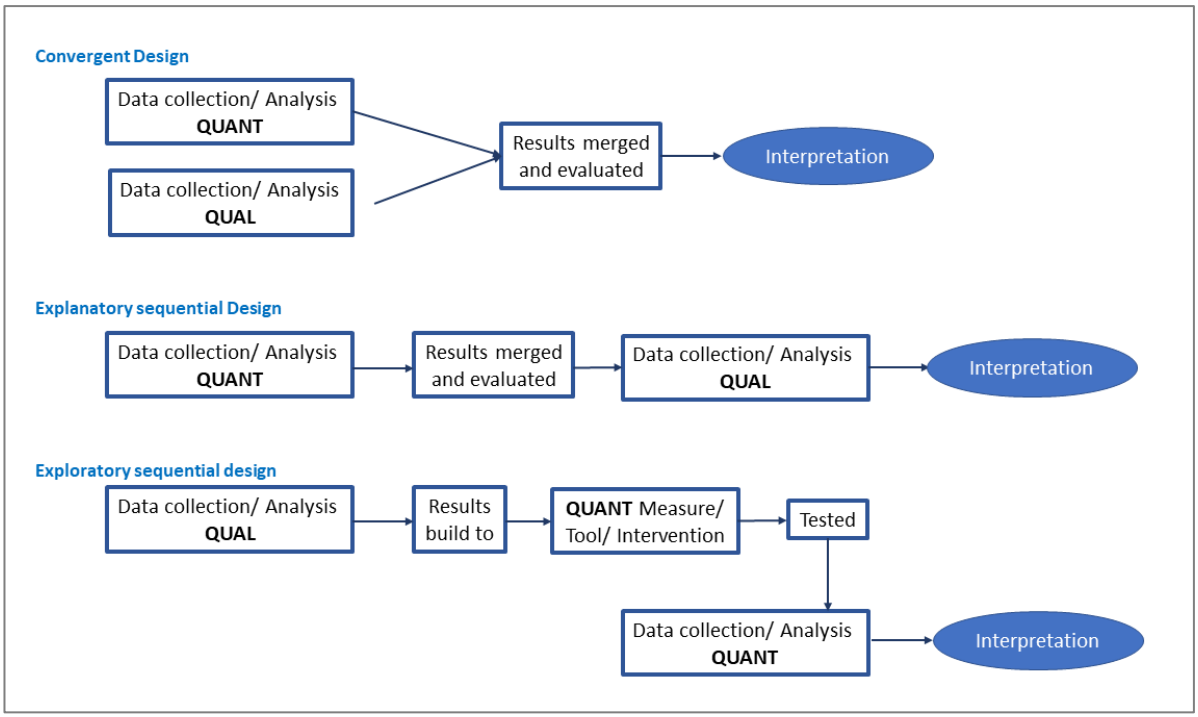


Figure 7: Mixed methods core design and data integration (199)

2.3.2 Data integration

Where and how the data integrates in the study design and overall analysis is an important methodological feature. Integration at the methods level is achieved through connecting, building, merging, or embedding datasets. Connecting is when one database links to another through sampling, such as in sequential designs. Building is when one database informs the data collection of the other such as in exploratory sequential designs. Merging is when databases are brought together for analysis such

as in convergent designs. Embedding is when the data collection and analysis link at multiple points such as in interventional sequential designs (204).

Data integration at the reporting level has been defined as occurring through a narrative approach (where quantitative and qualitative are presented in a single/series of reports); data transformation (where one type of data is converted to another) and through joint displays (where data is displayed in a visual means such a figure, table, matrix or graph) (204, 205). At the integration interpretation level, techniques need to consider the outcomes and fit of the data set against study aims and objectives. Different words, though similar in description, have been used by various authors to illustrate the observed relationships between quantitative and qualitative data integrated in this way (200, 204, 206):

- Convergence/Confirmation – the findings of both agree
- Complementarity/ Expansion – data diverges and expands insights or helps describe complementary aspects of a phenomena
- Discrepancy/ Discordance/ Dissonance – data appear to contradict each other or are inconsistent

2.3.3 Approach to mixed methods used in this study

Using the outputs from the development phase of the study, (the systematic review (Chapter 3), qualitative inquiry (Chapter 4) and theory building (Chapter 5)), the REMAP-Haemophilia feasibility study will use a fixed methods design with a convergent typology. Data integration will be carried out, presenting the data tabulated in a side by side/joint display to enhance the visualisation of the agreement between datasets. Descriptors used in the analysis of the data in this format will be Confirmation, Expansion and Discrepancy.

2.4 Philosophical considerations

Being cognisant of the potential philosophical conflicts in choosing to use a mixed methods approach requires the researcher to explicate the research paradigm in which the study is viewed, so that readers may fully understand the position taken and use appropriate criteria when judging the merits of that research (207). Thomas Kuhn suggested scientists work within a unified package of beliefs about science and scientific knowledge, which govern the research and practice in a particular field. He

referred to such beliefs a paradigm (208). Guba and Lincoln define a paradigm slightly differently, as a holistic and comprehensive perspective of the world and recognising the individuals place in it (209). This paradigm as a 'worldview', defining an encompassing perspective on the world is one favoured by Cresswell and Plano Clark (199), but one that also requires a clarification of the elements contained within that worldview (210). Whilst Kuhn considered a paradigm as a shared belief in a research field, others saw this from an anthropological view as problematic, as the diversity within individual identities is considered fundamental rather than superficial (211).

Paradigmatic assumptions function as a lens for viewing the world and are conceived as formulations of ontology and epistemology. Ontology is concerned with the nature of reality, that is, the nature of existence and the study of being. Epistemology is a way of understanding and explaining what we know, a theory of knowledge of what can be known and what criteria is used to justify it being knowledge (207, 208). Choice of paradigmatic position can be considered to exist along a spectrum of positivism at one end to constructivism at the other, whilst others such as post-positivism, pragmatism and critical realism are positioned between the extremes.

2.4.1 Positivism/ post-positivism

Viewed as the paradigm of the 'scientific method', positivism views reality as separate and independent from the researcher (199). Ontologically realist and situating itself as wholly objective, it is devoid of subjective meaning being attributed to the object under study, affirming that such objects have meaning prior to, and independently of, any consciousness about them (208). Epistemologically, knowledge of this reality is gained through observation (what is observed is thought to be real), with credibility then enhanced through replication of studies (207). However, whilst appropriate for identifying discrete cause and effect, the positivist preoccupation with robust methods and unquestionable statistical rules of enquiry are also seen to be problematic, as such a contrived and artificial view of the world makes it difficult, if not impossible to apply in real-world settings (212).

The more modern post-positivist approach is seen as a less arrogant form of positivism, and in acknowledging the role of values a researcher brings to data collection, it talks of probability rather than certainty, and seeks approximate truth

rather than absolute objectivity (208). The need to provide repeatable, objective, generalisable results leads positivist/ post-positivist enquiry to use mainly quantitative methods for data collection and analysis. This position was taken when undertaking the systematic review in Chapter 3.

2.4.2 Constructivism

At the other end of the spectrum constructivism, being ontologically idealist, views reality as being socially constructed and multiple. Epistemologically, knowledge of this reality involves actively looking for multiple perspectives and understanding the views of people in a particular situation (207, 208). In this paradigmatic view, there is no one true or valid interpretation, as meaning emerges from the individuals interaction with the object and how they relate to it (208). Unlike positivism, a key point here is that the researcher is considered an implicit part of the research process. The knowledge generated will bear the mark of that process, meaning such knowledge may be transferable to other situations but cannot be assumed to be generalisable (207). This bottom up research approach from individual perspectives to broad patterns is therefore associated with qualitative research methods such as interviews and focus groups (199). Constructivism was the position adopted for the qualitative study in Chapter 4.

2.4.3 Pragmatism

Pragmatism is a philosophical doctrine that denies the possibility of achieving authentic knowledge in regard to truth. In doing so it holds that in making do with plausible information adequate to practice, researchers should only deal with the facts as they exist in relation to the problem at hand (213). Such a view places pragmatists outside of a single defined ontological or epistemological stance. Pragmatists see research questions as not inherently important and methods are not automatically appropriate, as it is the researcher themselves who make those choices reflexively, looking toward what is chosen to study and how to do so (210). The attendance to the practical nature of what works in reality and associating truth with the solution to a problem, means that pragmatism is often cited as a natural philosophical home for the practice of physiotherapy, given its apparent affiliation to multiplicities of complex clinical presentations (209). Furthermore, the pragmatic worldview is used to defend the choice of mixed methods, using a pluralistic approach to multiple methods of data

to inform the research question at hand (199). However, others have criticized the use of pragmatism as a simplistic attempt to justify using a mixed methods approach (214). In agreement with Maxwell and Mittapalli (2010), this thesis takes a stance that assuming a pragmatic position underestimates the actual influence of philosophical assumptions on the choice of research methods.

2.4.4 Critical realism

Combining ontological realism (a real world exists independently of our perceptions and constructions) and epistemological constructivism, critical realism is a philosophy of causation that recognises the world is an open system with a constellation of structures, mechanisms and outcomes (215). Originally conceived by Bhaskar in 1975 (216), critical realism describes three ontological levels of reality and contends that epistemologically, there is no such thing as final truth. The three levels are:

- **the real**- existence of structures with generative powers (potential to produce something) and represents what happens when these powers are activated
- **the actual** – representing the portions of those events that take place in 'real' that may or may not be experienced by the relevant actor
- **the empirical** – relating to human perception and experiences of what happens

Critical realism places emphasis on both the observable reality as well as the potential contextual experiences of that reality, with mechanisms of outcomes stratified and described as physical, biological, social, cultural and behavioural (212, 215).

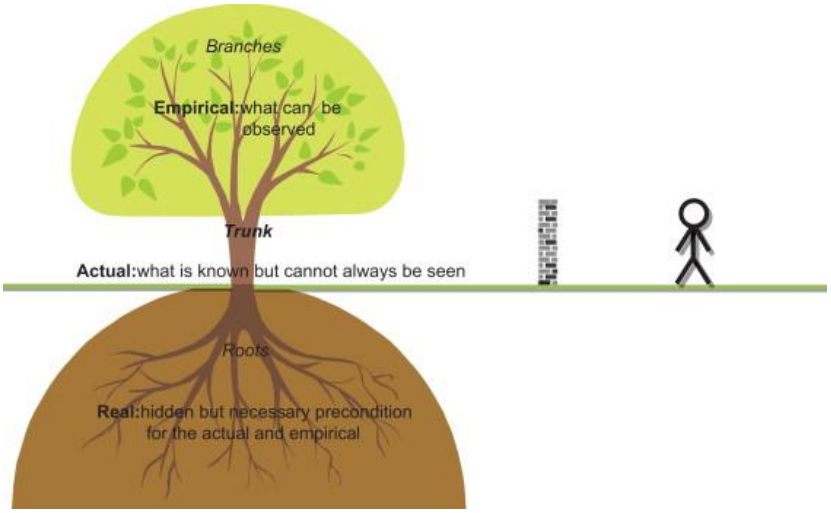


Figure 8: Visualisation of the three ontological levels of critical realism (From Walsh and Evans 2014) (217)

Similar to constructivism, critical realism posits that the researcher is involved and interacts with the data collected, and so does not view bias as something to be eliminated (218). This worldview fits well with a choice to use mixed methods, as it provides a philosophical stance that is compatible with the methodological characteristics of both quantitative and qualitative research and facilitates cooperation between the two (211).

2.4.5 The researcher as a critical realist

Whilst elements of pragmatism resonate with the approach used in this thesis, mainly the practicalities and immediate clinical potential of this pain management intervention, the early evaluative study design described here is better supported within a critical realist frame. The overall approach of the feasibility study was informed by extensive development work, as well as a key focus being the development of a stakeholder informed programme theory that was then used to create the study protocol. Such an approach can be considered an emergent, theory informed research approach and sits well within a critical realist research cycle. Figure 9 highlights the similarities of this approach to that of the overall complex intervention development design of this thesis (215).

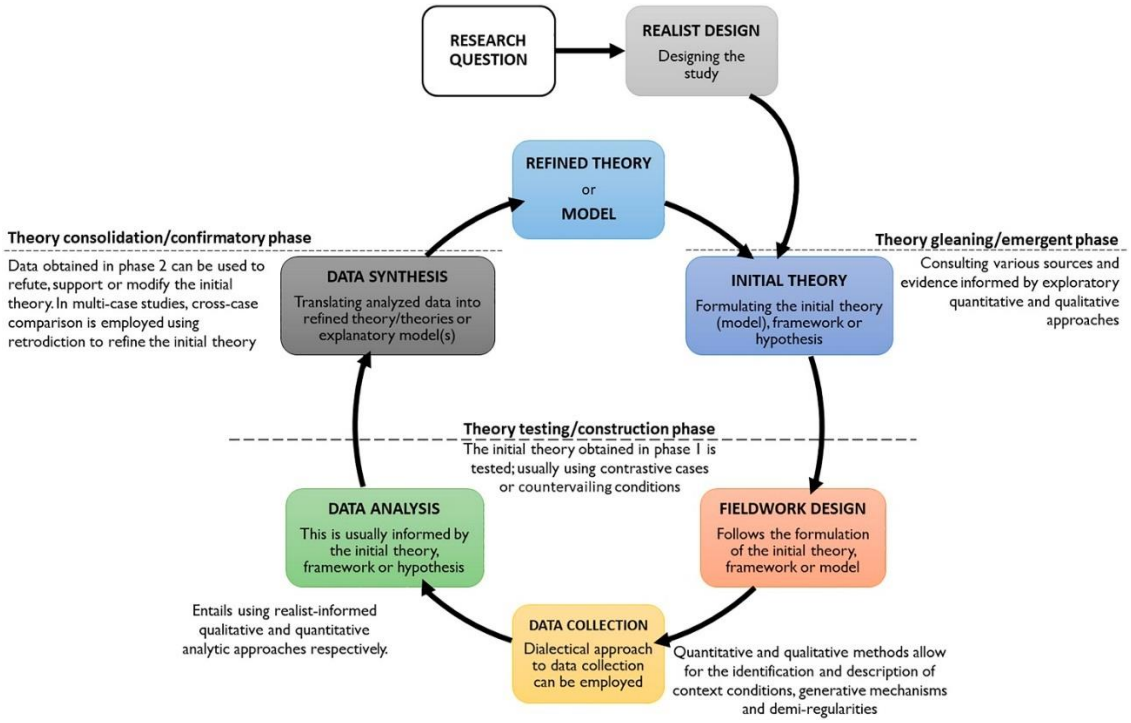


Figure 9: The phases of theory development within the critical realist research cycle (From Mukumbang, 2021)(215)

The significant limitations in previously published research studies of pain management strategies for PWH provide a further basis for the need to take a philosophically grounded theory development approach. The complexities of living with pain and its management require a tangible, coherent approach to knowledge creation. Retroductively creating an understanding of causal explanation, that an outcome can only be understood when both the context and the supposed mechanisms of effect have been better understood, is inherent in the critical realist position (i.e. mechanism + context = outcome) (219). Knowledge about health and illness does not need to be confined to any one particular methodological principle because illness operates in a number of different ways and reflects the different stratified contexts in which illness occurs (212). The incomplete nature of knowledge regarding pain as a concept and its management in PWH permits critical realism as an approach to acknowledging each account of experience as being valid, adding value to the developing theory of the phenomenon.

Table 3 presents an overview of the philosophical positions taken in each section of this thesis.

Table 3: Philosophical positioning within each section of the thesis

	Philosophical position	**Ontology**	**Epistemology**	**Axiology**	**Approach to theory**	**Method choice**
Chapter 3: **Systematic Review**	Post-Positivism	One True reality Universalism Granular	Scientific method Observed and measured facts	Value free research Objective stance from researcher	Deductive	Mono-method Quantitative
Chapter 4: **Qualitative Inquiry**	Constructivism	Socially constructed Multiple meanings	Phenomenon Focus on narratives/ perceptions/ interpretations	Value bound research Researcher part of what is researched	Abductive	Mono-method Qualitative
Chapter 6: **Feasibility study**	Critical Realism	Stratified reality Objective structures Causal mechanisms	Epistemological relativism Facts are social constructs Knowledge is historically situated and transient	Value laden research Researcher is as objective as possible	Retroductive	Mixed Methods Quantitative & Qualitative

2.5 Stakeholder participation in intervention development

In 2015, a report commissioned by the Director General Research and Development and Chief Medical Officer Department of Health detailed the vision of the NIHR around public involvement in research. That vision was to improve the health and wellbeing of the public and their communities, and was seen to exist on six principles that involved: (220).

1. Building on people's existing capabilities
2. Promoting mutuality and reciprocity
3. Developing peer support networks
4. Breaking down boundaries
5. Facilitating as well as delivering
6. Recognising people and their experiences as assets

Even with such a positive vision there has continued to be some confusion over the definition and operationalisation of public involvement, resulting in such approaches being seen as an add-on rather than implicit within the research delivery. Understanding why patients may want to get involved in research, such as helping others, contributing to scientific knowledge and wanting their lived experience and knowledge to influence research, highlights the need for their involvement to be integral from the start (221).

Stakeholder involvement is now considered a core element in intervention development, helping reduce research waste and avoid studies that may have limited clinical relevance to end users or clinicians (196, 222). Stakeholders have been defined as those that are targeted by an intervention, those involved in the delivery or development of an intervention and those whose personal/ professional interests are affected (196). Participatory approaches involving stakeholders across different disciplines and contexts have in turn created some confusion over terminology such as co-production, co-development, and co-design. In response Smith and colleagues (223) (2022) proposed a typology of co-production:

- Citizens' contributions to public services
    - This is less about co-producing research and more aligned to a process where members of the public contribute towards the effectiveness and efficiency of public services
- Integrated knowledge translation
    - This is a described as a collaborative process where academics work with 'knowledge users' (e.g., clinicians, industry, policy makers), that aims to bridge the gap between research and practice. However, it is not considered essential to require the inclusion of people with lived experience.
- Equitable and experientially-informed research
    - Here equitable partnerships between contributors are fostered and maintained collaboratively throughout the research process. The lived experience and knowledge of particular people and service users is considered essential.

Whilst the typology described above helps clarify the overall context of co-production as a concept, its practical application has been viewed as a principles-driven venture rather than one based on a fixed set of tools or techniques (224), all the while being mindful that no one approach offers a panacea (222). Those principles have been described as:

1. The co-production is adequately resourced
2. Power is shared and the research is jointly owned, and people work together in equitable partnerships
3. Include all perspectives and skills to ensure the team has all necessary knowledge and expertise
4. Reciprocity and mutuality are respected
5. Diversity is important
6. Relationships are built and maintained on mutual respect, dignity, trust, transparency, humility, and relational ethics

2.5.1 Service user participation in this study

The participatory approach used in this thesis fulfilled the 'Equitable and experientially-informed research' description of Smith and colleagues (223). Involvement of people with haemophilia was integrated even in the pre-design phase of the overall conceptualisation of the studies from the day-to-day clinical environment and in conversations with the patient association (The Haemophilia Society) (Figure 10).This level of participatory involvement uses those informal, serendipitous moments in a clinical interaction where patients share their wants and wishes about the management of their condition, and has been recognised as adding value to research development (225).

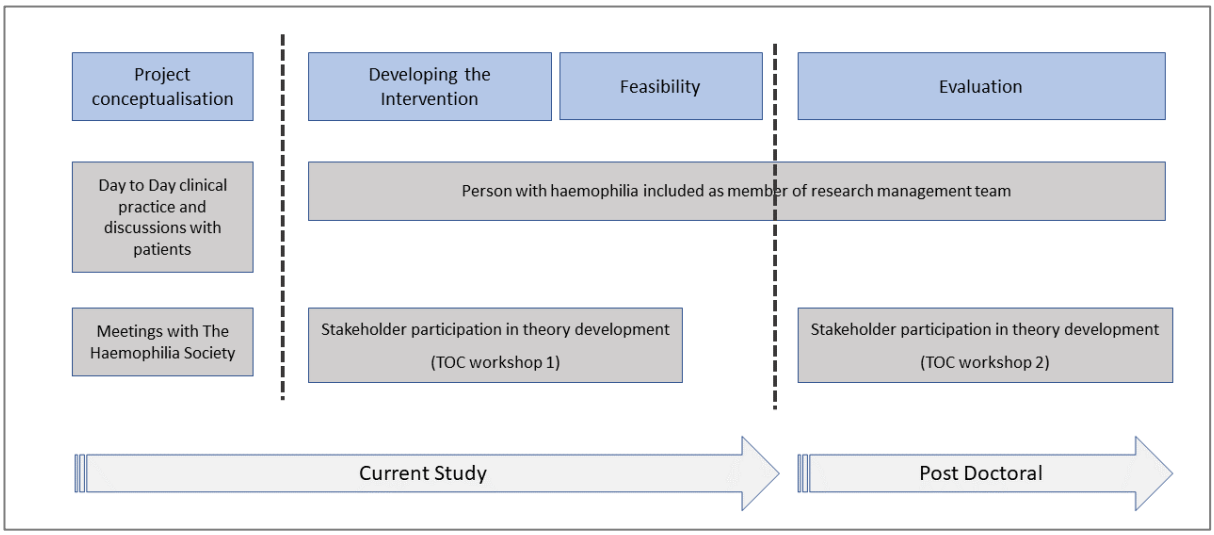


Figure 10: Stakeholder participation in the development of the REMAP-Haemophilia study

In a more formal manner, a person with haemophilia (CS) was approached and agreed to be a member of the research management group alongside the academic supervisors. CS was actively involved in the entire study process providing input at all stages of study design, participant facing documentation, study protocol and interview/focus group topic guides. Going forwards he will advise on dissemination of the study's findings to the wider haemophilia community in the UK.

This study also employed an innovative approach to the development of the programme theory for the feasibility study (Chapter 5). Three people with haemophilia and two specialist haemophilia physiotherapists agreed to participate in the theory of

change workshop, helping to create a meaningful intervention informed directly by their own unique experiences and views. A follow up theory of change workshop is planned to review the programme theory model against the findings of the study, and modifying any steps as required in further studies.

This chapter has described the philosophical position and methodological approach being used in this thesis, as well as how stakeholder participation will be used in the development of the REMAP-Haemophilia intervention. The next chapter will present the methods and results of the systematic review.

Chapter 3 - Systematic review

This chapter presents the methods and findings of a systematic review evaluating the current evidence for physiotherapy interventions for pain management in people with haemophilia. This specific and detailed approach to identifying and appraising the current evidence base is in keeping with the MRC frameworks guidance on the development of complex interventions. The systematic review presented in this chapter was accepted for publication following peer review in April 2020 (226). The text in this chapter therefore reflects that found in the publication (Appendix C), with additional detail included in this chapter where appropriate.

3.1 Introduction

People with haemophilia living with pain report limitations in mobility and independence, increased anxiety, poor quality of life, and frustration due to restrictions in activities of daily living (45, 121, 227). However, most recommendations for clinical management, including those from the World Federation of Haemophilia (WFH), mostly relate to pharmacological management of pain (68, 111, 124, 125, 228-230). Medical approaches that include prophylaxis with factor concentrate and prescription of pain medications, as well as physical medicine strategies including acupuncture, hydrotherapy, exercise and manual therapy have shown some positive effect on both acute and chronic pain (144, 230-232).

Although a widespread problem, there are no published clinical guidelines for the management of chronic arthritic joint pain in PWH. It has been recently highlighted that the use of physiotherapy and exercise is under-investigated, and trials should be designed to gauge its potential benefits for pain management (128, 233). In recent years there have been attempts to investigate a wide range of physiotherapeutic interventions for people with haemophilia who have a diagnosis of arthropathy. Previous systematic reviews in this area have focused on physical exercise or sport as an intervention whereby pain was not included as a primary outcome of evaluation (234-236), or where the review only focused on one joint (237).

3.2 Rationale for a systematic review

In developing a rehabilitation intervention that aims to influence arthropathic joint pain in PWH, it is important to be aware of other interventions that have been investigated. This serves to provide a background for the need for rehabilitation strategies, highlight what kind of interventions PWH may have been previously exposed to, and the degree of efficacy of interventions being tested. With the of goal reducing bias, a systematic review identifies, appraises and synthesises all relevant studies on a particular topic (238). It should define the research question, detail the sources searched with a reproducible search strategy, have clear inclusion/exclusion criteria, critically appraise and report the quality and risk of bias of studies, and have information about the data analysis and synthesis to allow reproducibility of results (239).

3.3 Aim of this systematic review

The aim of this systematic review is to evaluate and appraise the current evidence of the effects of a range of physiotherapy interventions on (1) pain intensity, (2) quality of life and (3) function in people with haemophilia.

3.4 Methods

3.4.1 Protocol and Registration

The methodological approach and analysis for this review was described in advance and documented in a protocol registered with the International Prospective Register of Systematic reviews (PROSPERO number: CRD42018116482). Reporting is in accordance with the PRISMA statement (240).

3.4.2 Eligibility Criteria

Study design for inclusion were those described as randomised controlled trials and quasi-experimental studies including controlled studies, before and after and interrupted time studies, comparing to no intervention/ routine care group, or between group comparison of one treatment intervention against another.

Studies describing any physiotherapy/rehabilitation/physical therapy intervention that had pain intensity, functional outcomes, and health related quality of life as outcome measures were included.

Participants of any age with a diagnosis of haemophilia (A or B) with any severity of the disease (mild, moderate, and severe) and/or haemophilic arthropathy were included. Those participants with a diagnosis of an inhibitor (anti-body to factor VIII or IX) and co-morbidities were not excluded. There was no restriction in country or care settings for studies. Studies that investigated joint disease or pain as a result other inherited bleeding disorders such as von Willebrand disease were excluded.

3.5 Information Sources

A systematic search of the literature was conducted on 07/09/2018 by the researcher. The approach used was as follows:

1. AMED (EBSCO), CINAHL (EBSCO), EMBASE (OVID), MEDLINE (OVID) and PEDro
2. Cochrane central register of controlled trials
3. Trial registries – clinicaltrial.gov, international trials registry, EU clinical trials register
4. Grey literature
5. Hand searching key journals
6. Checking reference lists of previous related systematic reviews in haemophilia
7. Hand searched abstract book of EAHAD congress (European Association of Haemophilia and Associated Disorders) 2000-2018 and WFH (World Federation of Haemophilia) world congresses 2000-2018

Only those studies that were fully published and in the English language were included.

3.6 Search Strategy

The search strategy used across each database is detailed in Figure 11. Iterative refinement of the search strategy was achieved after multiple practice searches using potential search terms and associated subject headings. The university version of OVID and EBSCO search platforms maps to subject headings by default. The search strategy was discussed in detail and endorsed by the University librarian (AE-J).

Database/register	Search years	Search terms
AMED (EBSCO)	1985- present	#H(a)emophilia AND physio*/ physical*-therapy
CINAHL (EBSCO)	1961- present	#H(a)emophilia AND physio*/ physical*-therapy
EMBASE (OVID)	1976- present	#1 exp h*emophilia #2 exp pain #3 1 AND 2 #4 exp physio*/physical*-therapy #5 exp manual therapy or exp manipulative medicine #6 exp hydrotherapy or exp "aquatic exercise" #7 exp electrotherapy or exp "electrophysical agents" #8 exp rehabilitation or "home rehabilitation" or "rehabilitation medicine" or "exercise supervised" or "exercise unsupervised" #9 exp "patient education" #10 4 or 5 or 6 or 7 or 8 or 9 #11 3 AND 10 #12 "randomi*ed controlled trial" or "controlled trial" or randomi*ed #13 11 AND 12 (filter limits Full Text and English Language)
MEDLINE (OVID)	1964- present	
PEDro		#H(a)emophilia
www.clinicaltrials.gov		#H(a)emophilia AND physio*/ physical*-therapy
International Trials registry http://apps.who.int/trialsearch/		#H(a)emophilia AND physio*/ physical*-therapy
EU Clinical Trials Register www.clinicaltrialsregister.eu		#H(a)emophilia AND physio*/ physical*-therapy

Figure 11: Search strategy for each database used in the systematic review

3.7 Study Selection

One reviewer (PML) independently carried out the search strategy on the listed databases. Results from each database search were saved, duplicates were removed and then imported to the Rayyan platform (241). The Rayyan platform is a free, web-based application that expedites the initial screening of abstracts using a process of semi-automation (241). It allows multiple reviewers to independently review and check titles and abstracts whilst blinded from each other. Two reviewers (PML and DS) reviewed the abstracts. Once each reviewer had completed their check, PML was able to undo the blinding and compare those which had been accepted, rejected and were undecided by both reviewers. Those articles highlighted as discrepant between

reviewers were then discussed further and consensus was reached without the need for a third reviewer.

Full texts of agreed abstracts were then retrieved and evaluated independently by PML and DS to determine if they were eligible for inclusion in the systematic review.

3.8 Data Collection Process

A data extraction proforma was developed using the template from the Cochrane group as a guide (Appendix A). One reviewer (PML) extracted the data from the included studies, and a second reviewer (DS) checked the extracted data for accuracy. One author was contacted for further information and data was received from them (242).

3.9 Data items

Information extracted from each trial included type of study design, participant information, interventions, comparison interventions (if appropriate), outcome measures (pre and post intervention as well as follow up if available), results including pain, function, and quality of life. Assumptions were made about the location of study interventions if it was not explicit in the study description. No other assumptions were made.

3.10 Risk of bias in individual studies

The Cochrane Risk of Bias assessment tool was used to assess each included paper. Criteria of unclear, low, or high risk of bias were assigned against selection bias, performance bias, detection bias, attrition bias, reporting bias and any other identified bias.

3.11 Methods of analysis

Review Manager 5.3 (RevMan5.3) was used to collate and analyse study data. It is the free to use software available from The Cochrane Collaboration for compiling systematic reviews and meta-analysis (243).

As all outcomes being analysed were continuous variables, the mean change from baseline to follow up and the standard deviation of the mean difference from the results in each study were calculated and input into RevMan. Using a fixed effects model, these figures plus the number of participants per arm per trial, allowed the

mean differences and the 95% confidence interval to be calculated and displayed visually in a forest plot. A fixed effects model was chosen for analysis, as a random-effects model when used with small studies (such as all those included in this review) can over estimate effect due to added weight being assigned to small studies (244).

Focussing only on the stated outcomes of pain, function, and quality of life where available, studies were grouped into a) physiotherapy intervention versus no intervention and b) physiotherapy intervention A versus physiotherapy intervention B.

A narrative synthesis of the evidence was completed and included the use of the GRADE approach. GRADE is a system of grading the quality of evidence (Appendix B). It is transparent and systematic in its approach, and requires that explicit judgements are made about the importance of each outcome in any recommendations on that evidence (245). The GRADE system uses 8 criteria against which to assess the quality of evidence as either high, moderate, low or very low. The criteria are 1) risk of bias, 2) inconsistency, 3) indirectness, 4) imprecision, 5) publication, 6) other (a. large effect, b. dose response, c. no plausible confounding – only these assessments permit an upgrade). All outcomes start on 'high' quality (those studies not an RCT, start score process on 'Low'). They may then be downgraded one level per criteria if it is deemed to have a serious risk (-1) or very serious risk (-2) (246).

3.12 Additional analysis

No additional meta-analysis was indicated due to clinical and statistical heterogeneity within the included studies.

3.13 Results

3.13.1 Study selection

The process of study identification and selection for inclusion in the review are presented in Figure 12. Database searching identified 416 citations. Searching published reference lists yielded one additional reference. The search of trial registries including clincialtrial.gov, international trials registry and the EU trials register, and handsearching of conference proceedings yielded no other references.

Following screening for, and removal of duplicates, 309 references remained. Review of abstracts resulted in removal of 290 as they did not meet the inclusion criteria. Nineteen full text articles were assessed for eligibility, and of these, 10 were removed (3 were background articles, 1 was protocol paper, 1 was a survey, 2 had physiotherapy as secondary intervention, 1 did not have pain as an outcome, 2 were not relevant).

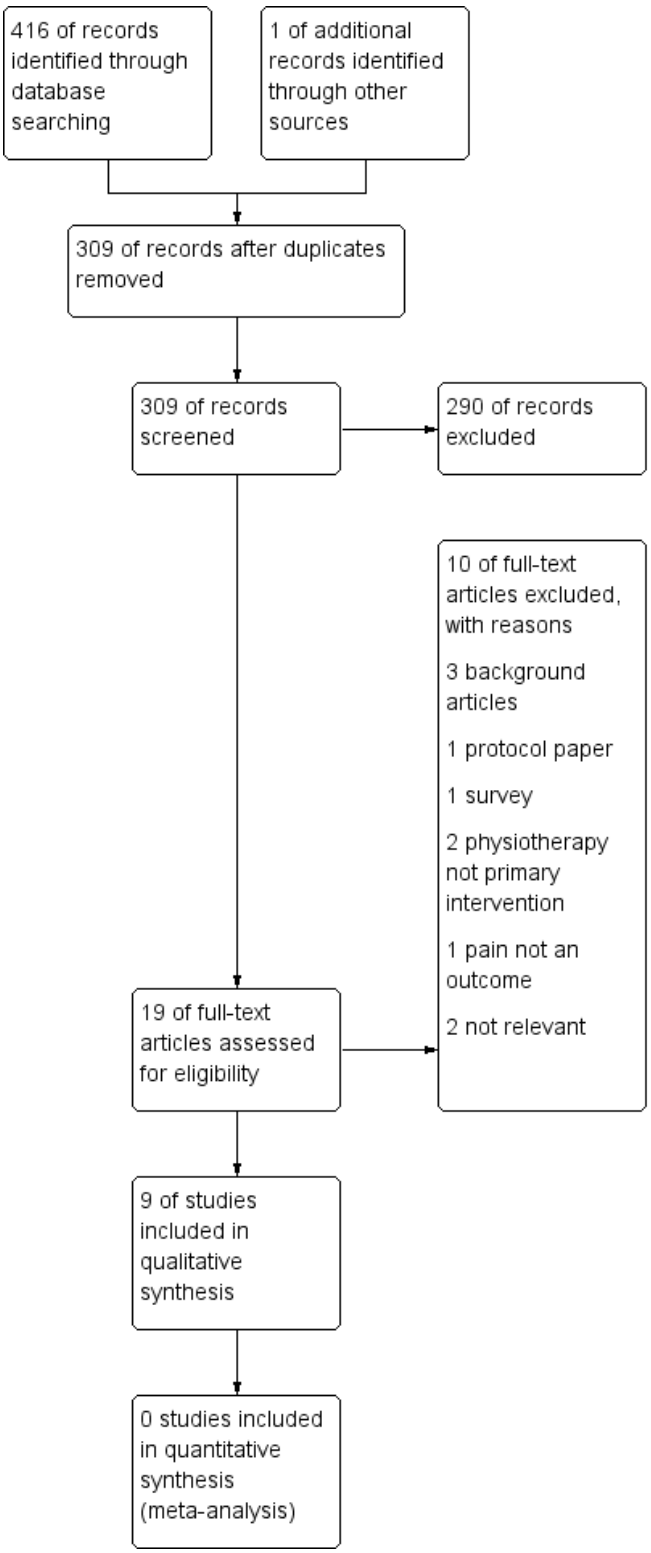


Figure 12: Prisma flow chart of study identification and selection for inclusion in review

3.13.2 Study characteristics

A total of 9 studies involving 9 trials were identified (Table 4). The number of participants per study ranged from 9 (232) to 40 (231). The total overall number of participants included across all included studies was 235. Of these, 60 were children (aged 9-13) and 175 were adults (aged 26-58). Severity of haemophilia was not specified for 70 participants. Of the remaining 165, 93 were identified as having a diagnosis of severe haemophilia, 50 moderate, 17 mild and 5 mild/moderate.

Table 4: Summary of characteristics of studies included in systematic review

Study	Methods	Participants	Intervention	Outcomes and measures	Notes
Cuesta-Barriuso 2014 (232)	Quasi-experimental pre-post design	9 Adults with haemophilia A or B (Mean age 35.8) and arthropathy in one or both ankles on prophylaxis. 3 bilateral ankle arthropathy, 5 with right ankle arthropathy and 1 with severe arthropathy left ankle. Severe (n=8) Moderate (n=1) Randomised into 2 groups: A: Passive joint mobilisations (n=4) B: Manual therapy (n=5)	6-week study period 2 hours per week (both groups) Both groups: infrared lamp start of session Group A: passive joint mobilisations and muscle exercises and proprioception. Group B: had manual therapy (joint distractions) and muscle exercises and proprioception Both groups cryotherapy to finish session	Pain intensity ankle: VAS HR QoL: A36 Hemophilia QoL questionnaire Ankle ROM: Dorsi-, plantar-flexion, inversion, eversion Proprioception: Romberg's test	Not stated what baseline was for participants in each group (i.e., how many ankles (uni-or bilateral) - were affected in each individual)
Cuesta-Barriuso 2014 (247)	Randomised control pilot study	31 adults with haemophilia (mean age 35.29) and ankle arthropathy (6 unilateral and 25 bilateral arthropathy) Severe (n=19) Moderate (n=12) Randomised into 3 groups: Manual Therapy (n=11) Education (n=10) Control group (n-=10).	12 weeks study period Manual Therapy group: 2x 60 mins per session per week Thermotherapy, ankle joint traction, passive muscle stretching gastrocnemius, Isometric and resisted exercises, proprioception exercises, local cryotherapy. Education and exercise group: (6 x 90 min sessions once a fortnight).	Calf Strength: Calf circumference Ankle ROM : Dorsi-/plantar-flexion, inversion, eversion Ankle pain: VAS	Authors note that there were differences between the groups in terms of radiological deterioration, ROM and pain perception. Potential variance between groups associated with severity of haemophilia. Control group had mostly moderate and on-demand treatment participants, whereas

			Theory: ankle anatomy/biomechanics, joint bleeding, synovitis, and arthropathy, proprioception, pain and mobility Practical: Ankle ROM exercises, strengthening exercises, exercise for mobility and pain management, proprioception exercises. Encouraged to walk, cycle and swim. Group support and Q&A feedback throughout.		both intervention arms had mostly severe and on prophylaxis. Participants handed records of home exercise compliance in every 2 weeks - but it was not stated if these were fully complete.
Cuesta-Barriuso 2017 (248)	Randomised controlled trial	20 adults with haemophilia (mean age 30.95) with at least one joint affected by haemophilic arthropathy. Severe (n=10) Moderate (n=3) Mild (n=7) Randomised to 2 intervention arms – (1) control (n=10) (2) education with home exercise programme (HEP) (n=10)	15-week study period Educational sessions every 2 weeks for 60 mins alongside home exercise programme: Control group advised to continue with the same daily professional and sporting routines that they had been following Education/HEP: Theory: anatomy/biomechanics elbow, knee and ankle joints, haematoma management, exercise theory, joint bleeds, synovitis and arthropathy, proprioception, physical activity and sport.	Orthopaedic joint assessment: Gilbert Score Pain intensity ankle, knee, elbow: VAS Quality of life: A36 questionnaire Illness behaviour questionnaire (IBQ).	This appears to be the same group of participants that have already been enrolled in all of the authors previous papers. (? bias of results if participants have been exposed to previous interventions).

			Practical: muscle stretching for the upper and lower limbs, strengthening exercises for quadriceps, hamstrings, biceps/triceps and calves, proprioception exercises, encouraged to do 20 min walk per day.		
Cuesta-Barriuso 2018 (242)	Single blind randomised study	27 men with haemophilia (mean age 34.48 years) and elbow joint arthropathy Severe (n=17) Mild (n=10) Randomised to 3 groups- Manual therapy (n=9) Education (n=9) Control (n=9)	12-week study period Follow up assessment 6 months after end of intervention. Manual therapy group 2x 60 mins per session per week: Thermotherapy, elbow joint traction, elbow muscle stretching, joint compression technique, passive muscle stretching biceps/triceps, PNF of upper limb, local cryotherapy. Education group (90 mins session every 2 weeks, plus home exercise programme 20-30 mins daily): Theory: anatomy/biomechanics of elbow, haematoma management, joint bleed, synovitis, arthropathy, proprioception, physical activity and sport. Practical: Elbow ROM exercises, strengthening exercises, exercise for mobility and pain	Safety of intervention Elbow ROM: Flexion/ extension Arm circumference Biceps strength Pain intensity elbow: VAS	Baseline imbalances between groups: more people with mild haemophilia in the control group (6) than the Manual therapy group (1). Median VAS at baseline in education and control group was 0. Results presented in median and IQR instead of mean and SD - emailed authors to request data in mean/SD which was made available.

			management, proprioception exercises Control Group: usual routine		
Donoso-Ubeda 2018 (249)	Non-randomised, controlled before and after trial	16 men with haemophilia (mean age 40.69) and haemophilic arthropathy of the knee and ankle. Severe (n=12) Moderate (n=4) 2 groups: Fascial therapy (n=8) Control (n=8)	3-week study period 3 x 50-60 mins session per week. Control: advised to maintain same level and conditions of physical work and activity. Intervention arm: Fascial therapy No description given of patient position. All manoeuvres done on both lower limbs except thoracolumbar technique. Superficial and deep fascial release techniques.	Joint health: Haemophilia joint health score 2.1 Hamstring flexibility: Finger to floor test Lumbar mobility: Schober test Pain intensity right and left knee and ankle in weight and non-weightbearing: VAS	No randomisation
Eid 2015 (250)	Randomised Trial	30 boys with haemophilia (aged 9-13), with a bleed frequency in their knees of at least once a week. Moderate (n=30) Randomised to 3 groups: Low level laser therapy (LLLT) (n=15) Pulsed electromagnetic field therapy (PEMF) (n=15)	12-week study period Both Interventions: 3 times per week. Both groups had a physiotherapy programme as well as the study intervention. LLLT: applied to 5 points including medial and lateral side patellar tendon, medial and lateral side knee adjacent to patella and over suprapatellar pouch. Applied for 40sec to each point.	Pain intensity knee: VAS ROM knee Flexion/ Extension Swelling: Tape measure around knee Physical fitness: 6 minute walk test (6MWT) Laboratory investigations:	Poor description of intervention especially the physiotherapy programme. It was unclear when the laser was delivered in the session. There are ethical concerns about why the investigators would expose both knees to PEMF as it did not state if both were affected

			PEMF: solenoid adjusted to be over both knee joints. Parameters of treatment programme selected and adjusted as a frequency of 15Hz, intensity of 20 gauss for 20 mins. Physical therapy program: In acute haemarthrosis: cold packs, isometric exercises. In subacute: isometric and isotonic exercises given additionally. Chronic arthropathy: hot packs, strengthening, proprioception and stretching exercises. All groups had a home programme.	Erythrocyte sedimentation rate Complete blood count including white blood cells	(when the LASER group only treated one knee). Unclear if rate of haemarthrosis continued to be once per week throughout intervention period. No description of how acute, sub-acute haemarthrosis was assessed.
El-Shamy 2016 (251)	Single-blinded, placebo controlled randomised trial	30 boys with haemophilia (aged 9-13) with bilateral knee haemarthrosis. Severity of haemophilia not stated. Randomised into 2 groups: Laser therapy (n=15) Sham Laser group (n=15)	3 month study period. 3x 1 hour sessions per week. Both groups: received a 'traditional' physiotherapy programme that included hot packs, muscle stretching and strengthening exercises, proprioceptive training, balance and gait training. Laser group: Laser from HIRO device. Positioning: knee flexed to 30 degrees. Initial phase performed with fast scanning for total of 400J.	Pain intensity knee: VAS Functional capacity: 6MWT Gait assessment: Stride length, step length, velocity and cadence - using GAITRite system	

			Intermediate phase – applied hand piece to total 10 points (3 in medial knee, 2 in lateral knee and 3 above patella, and 2 below patella) with a fluency of 10mJ/cm^2 and a time of 14s at each point for a total of 150J. Final phase – same as initial phase, except that slow manual scanning was used with a total energy of 200J. <u>Sham Laser group:</u> HILT machine switched on with a visible light beam only - all parameters set up without switching the start position of the machine		
Goto 2014 (252)	Prospective, controlled, randomised non blind comparative stud	32 men with haemophilia (mean age 41.8) with arthropathy in knees or ankles. Recruited across 4 sites Severe (n=27) Moderate/mild (n=5) Randomised into 2 groups: Home exercise programme with self-monitoring (n=16) Home exercise alone (n=16)	8 weeks study period. <u>Both groups</u>: given home exercise programme. Only difference is the participants in the intervention arm could review their progress on their monitors, whereas the control arm group could not. <u>Home exercise programme</u> - guidance about strengthening knee extensors, static stretching for knee flexors, and standing balance training. Advice on promotion of physical activity given by physio to improve knee function.	Self-efficacy for exercise questionnaire: Questionnaire not stated Exercise adherence questionnaire: Questionnaire type not stated Quadriceps strength: using handheld dynamometer ROM: Ankle – plantar-, dorsiflexion Knee – flexion/ extension	Baseline imbalances of participants joint disease - ankle arthropathy was a much worse issue in the whole cohort even though the exercise plans carried out by participants was aimed at improving knee function. Unclear who delivered the programme to intervention group across the 4 sites and how the programme was delivered.

			Knee extension strength training, static stretches, and balance training Advice on leading an active life and doing non-contact sports were recommended for improving physical activity. ** Physiotherapist recommended the exercise most appropriate to the physical condition of each patient to be done 10 times per day. <u>Self-monitoring:</u> Participants were equipped with display activity monitors and feedback system via internet and mobile phone. When participants accessed the server to data input – feedback results appeared with time in form of graphs and tables. The number of times performed exercises, physical activity, bleeding frequency and injection of factor were recorded	Function: Modified functional reach test 10m gait time Pain intensity: VAS Physical Activity levels – using activity monitor	
Mazloum 2014 (231)	Quasi-experimental and prospective trial with a non-randomised pretest-posttest control group	40 people with haemophilia under 50 years old with impaired knee joint ROM. All severities – although exact numbers not stated. Randomised to 3 groups:	4-week study period. <u>Hydrotherapy:</u> Warm up (5mins) – co-ordinated and rhythmic movement of lower limb in water. Exercises (30-45mins) for hamstrings stretching, quadriceps strengthening, from isometric to	Pain intensity knee: (VAS) Knee ROM: Flexion and extension	Number of sessions per week was not stated. 43 participants started study, but 3 dropped out.

		Hydrotherapy (n=14) Land based exercise (n=13) Control Group (n=13) (Average age in each study group= 33 years)	isotonic. Cool down (5 mins) gentle stretching. <u>Land based exercise:</u> Warm up (5 mins) simple stretching exercises for muscles surrounding knee. Main part (30-45) hamstrings stretching, quadriceps strengthening, progressing from isometric to isotonic. Cool down (5 mins) of gentle stretching. <u>Control:</u> Not stated what was advised.		

3.13.3 Interventions

Study intervention periods ranged from 3 to 15 weeks. Four trials had a RCT design (231, 242, 247, 248).

Four studies compared one physiotherapy intervention against another. They included passive joint mobilisations and exercise versus manual therapy and exercises in adults with haemophilic ankle arthropathy (232); high intensity laser therapy (HILT) and exercise versus pulsed electromagnetic field and exercise in treatment of knee haemarthrosis in children (250); a home exercise programme and self-monitoring versus home exercise alone for haemophilic in adults with knee and ankle arthropathy (252); and HILT and exercise versus placebo HILT and exercise in haemophilic arthropathy of the knee in children (251).

Three studies in adults compared two physiotherapy intervention arms against a control group. They included one arm comparing the effect of manual therapy and exercise against a second of patient education and exercise in haemophilic ankle arthropathy (247), with the same study design being replicated again for elbow arthropathy (242). A third study investigated hydrotherapy against land based exercise with a control group in haemophilic knee arthropathy (231).

Two studies in adults compared one physiotherapy intervention with a control group. They included a study comparing patient education and home exercises with a control on elbow, knee and ankle haemophilic arthropathy (248), and a second comparing the effect of fascial therapy with a control group on knee and ankle haemophilic arthropathy (249).

One study performed the intervention 3 sessions per week for three weeks (249), with another not stating how many sessions were performed over four weeks (231). Two studies performed the intervention for 2 sessions per week for 6 weeks (232, 242) and one study encouraged participants to do exercises 10-times a day for 8 weeks (252). Another performed 2 sessions per week over 12 weeks (247) with another doing 1 session every 2 weeks for 12 weeks (242). The participants in two studies received 3 sessions per week for 12 weeks (250) and another one session every 2 weeks for 15 weeks (248).

3.13.4 Risk of Bias

Risk of bias was assessed for each study by two authors independently (PML and DS). Assessment of risk of bias found agreement between study authors was moderate (Cohen's K 0.51). All the included studies had an overall risk of bias. (Figure 13 and 14)

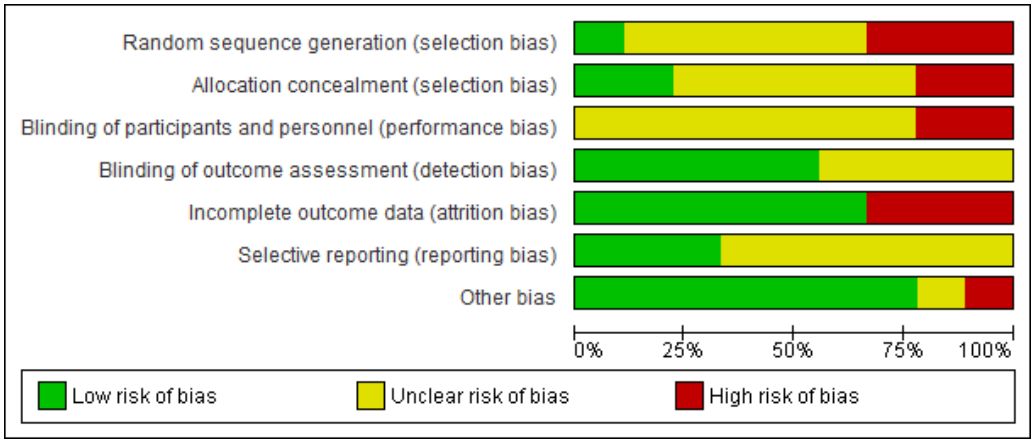


Figure 13: Risk of bias graph - author assessed risk of bias across all studies

3.13.5 Sequence generation

Only one paper rated low risk for sequence generation as it described the use of a random number generation table for each participant (252). Six studies were assessed as having an unclear risk of bias as sequence generation methods was not described. One paper rated high risk as participants were chosen for inclusion based on geographical location (249).

3.13.6 Allocation concealment

Two studies had a low risk of selection bias with both describing opaque envelopes being distributed by someone unrelated to the study (242, 248). Six studies were rated unclear due to lack of detail on methods of concealment. One study rated high risk as participants were selected based on geography (249).

3.13.7 Blinding

Blinding of participants was not done in any of the included studies, and none of the study personnel were blinded in any study. Blinded evaluators were used to assess

outcomes in five studies (232, 242, 247, 248, 250) were rated for low risk of bias. Two studies rated unclear as they did not state if outcome assessment was blinded (231, 251) and two rated high risk as outcome assessment was completed by the same individuals delivering the intervention (249, 252).

3.13.8 Incomplete outcome data

Four studies rated as low risk of attrition bias as all stated that all participants completed the intervention (232, 242, 248, 252). Five rated as unclear as although they did not report dropouts, they also did not explicitly state that all had completed the intervention (242, 247, 249-251). One study was rated as high risk as although the authors reported three dropouts, they did not specify from which group they came (231).

3.13.9 Selective reporting

Three studies were rated as having a high risk of selective reporting bias. One study failed to report on changes to bleeding frequency even though this was an inclusion criteria for the study(250). Another describes an improvement in joint health with the Haemophilia Joint Health Score but includes no data to support this (251) and another does not report on all of the elbow joints included in their study(242). The six other studies were determined to have an unclear risk of selective reporting bias.

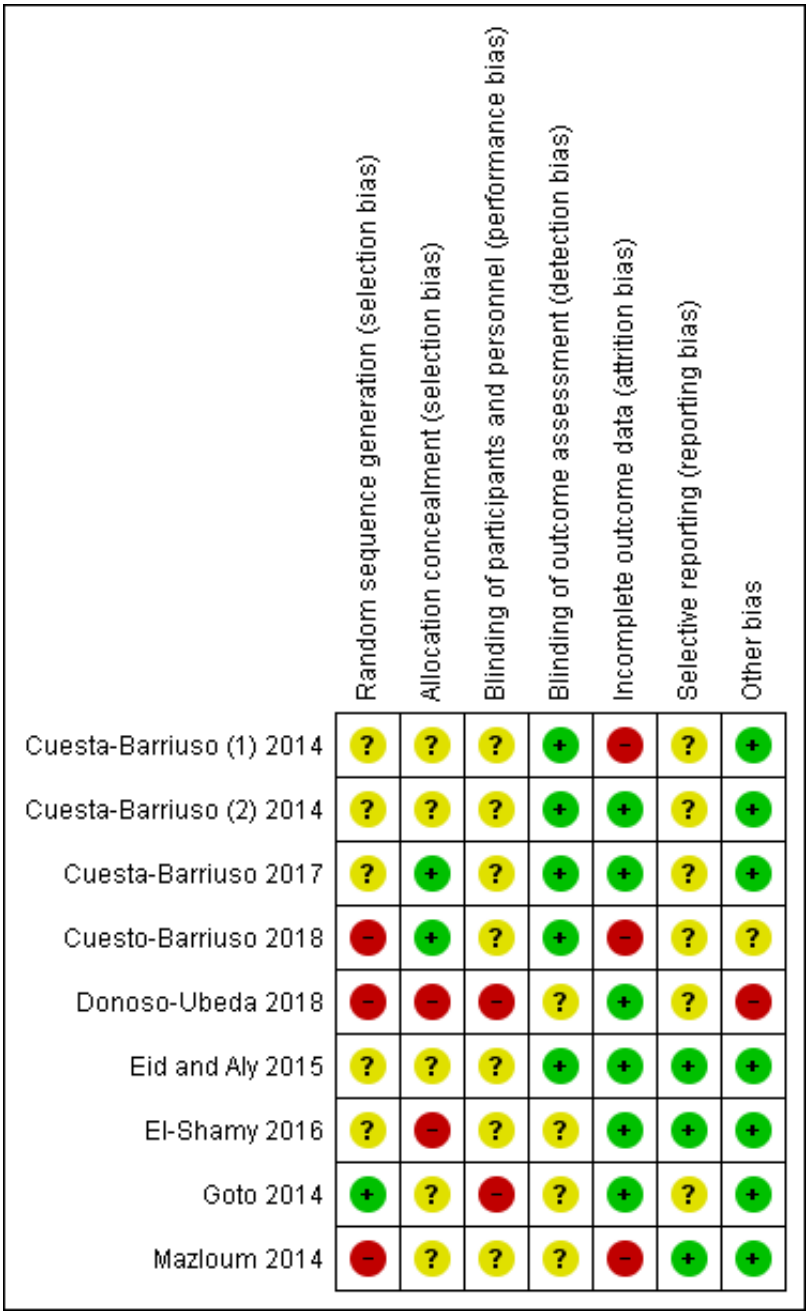


Figure 14: Risk of bias summary – author assessed risk of bias for each study

3.13.10 Data Synthesis

All the outcome measures used in each of the nine included trials are presented in Table 4. Although there were multiple outcomes measured across the trials, for the purposes of this review only those of pain intensity, quality of life and functional capability are included in this qualitative synthesis.

Due to large variations in study design, participants and interventions, meta-analysis was not possible. The results are described qualitatively with mean difference and confidence intervals provided, as well as using the GRADE approach for evaluation of the quality of the evidence and strength of recommendations (246).

Data presented in this review apply only to the immediate post intervention assessments, that is, before and after data. Data for those studies that also included 3 or 6 month follow up periods was not included as part of the review. All nine studies included an assessment for pain using the visual analogue scale (VAS). Two trials assessed health related quality of life (HR-QoL) using the A36 Haemophilia-QOL questionnaire (232, 248). Physical function was assessed in two studies with the 6-minute walk test (6MWT) (250) and with the 10 meter walk test (10MWT) and a modified functional reach test in one study (252). None of the other studies measured function or HR-QoL.

If a trial was comparing two types of physiotherapy intervention against a control, the results from each intervention were analysed individually against the control (physiotherapy intervention versus no intervention), as well as against each other when comparing one intervention with another (A versus B).

3.13.11 Physiotherapy versus no intervention

Five studies were included in this comparison (231, 242, 247-249) and the forest plot results are presented below in Figure 15.

3.13.11.1 Primary outcome - Pain

All five trials included assessment of pain intensity using the visual analogue scale (VAS), with improvement in pain reported as a decrease in the VAS score. All were conducted on adults over 18 years of age, and apart from one study (249) which was a

non-randomized controlled trial, all were RCT's. All studies provided low to very low quality evidence for the effect of physiotherapy interventions on the management of pain, quality of life and function.

One Cuesta-Barriuso study (2017)(248) investigated the effects of patient education and home exercise programme (n=10) compared to no intervention (n=10) on pain intensity in elbows, knee and ankles. The intervention consisted of education on joint anatomy, joint bleeding and management, proprioception, and physical activity. The home exercise components, advised to be done twice a day, included range of motion, isometric and proprioceptive exercises, as well as encouragement to do 20 minutes walking per day. It is not clear if there is any beneficial effect of the intervention versus the control group for pain intensity in the knee, MD -0.75 VAS (95% CI -2.13 to 0.63) or the ankle, MD -0.55 VAS (95% CI -2.37 to 1.27). MD and CI for the elbow were not estimable.

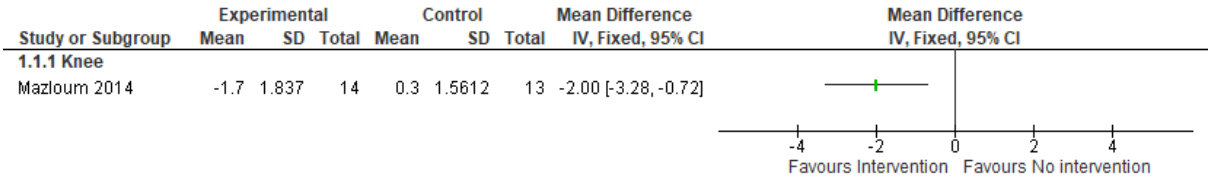
A second Cuesta-Barriuso study (2014) (247) investigated the effect of manual therapy and exercise (n=11) or patient education and home exercise (n=10) versus no intervention (n=10) on pain intensity in haemophilic arthropathy of the ankle. The education component was exactly as that already described above, but specific to the ankle. The manual therapy and exercise arm consisted of thermotherapy to start, joint traction, passive gastrocnemius stretching and relaxation, isometric and resisted exercises and proprioception exercises, and cryotherapy to finish the session. It is not clear if there is any beneficial effect on ankle pain with manual therapy and exercise versus no intervention, MD 0.06 VAS (95% CI -1.47 to 1.6) or with patient education and home exercise versus no intervention, MD -0.3 VAS (95% CI -1.2 to 0.6).

A third Cuesta-Barriuso study (2018) (242) again investigated the effect of manual therapy and exercise (n=9) or patient education and home exercise (n=9) versus no intervention but on pain intensity in haemophilic arthropathy of the elbow. Both the manual therapy and education intervention arms were exactly the same as the previous study in 2014. It is not clear if there is any beneficial effect on elbow pain with manual therapy and exercise versus no intervention, MD -0.30 VAS (95% CI -0.92 to 0.32) or with patient education and home exercise versus no intervention, MD -0.01 VAS (95% CI -0.34 to 0.36).

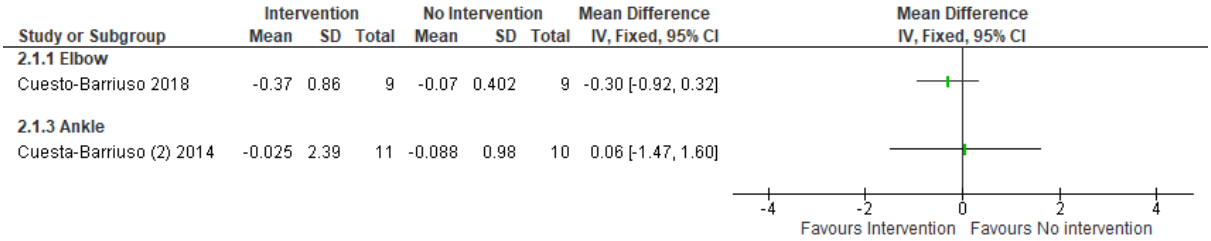
In a study with high risk of bias, Donoso-Ubeda and colleagues (2018) (249) investigated the effects of fascial therapy on pain intensity in knees and ankles with haemophilic arthropathy. The intervention of 3 sessions over 3 weeks, consisted of the application of fascial release and mobility techniques to the lower limbs and thoracolumbar area (n=8). A non-randomised control group, allocated on geographical location (n=8) received no intervention. Although the study reported weightbearing and non-weightbearing VAS pain scores for the ankle and knee on both the right and left legs, only those scores in non-weightbearing were included in analysis here. Results for the left ankle and knee were not estimable. It is not clear if there is any beneficial effect of the intervention on right knee pain intensity, MD -0.87 VAS (95% CI -2.81 to 1.07). There is a small positive effect of the intervention on right ankle pain intensity, MD -0.76 VAS (95% CI -1.39 to -0.13).

The study by Mazloum et al (2014) (231) investigated the effect of hydrotherapy (n=14) or land based exercise (n=13) versus no intervention (n=13) on pain intensity in the knee of people with haemophilic arthropathy. The study period was 4 weeks, although the number of sessions for either arm was not stated. The hydrotherapy intervention (45-55mins) consisted of rhythmic movements in water, quadriceps strengthening, hamstrings stretches, isometric to isotonic muscle exercises and stretching to finish. The land-based exercises (45-55 mins) were described as being the same as those in the water. The control group received no intervention. Both interventions were beneficial to knee pain intensity compared to no intervention. Hydrotherapy versus no intervention had a slightly stronger effect on pain intensity, MD -2.0 VAS (95% CI -3.28 to -0.72) compared to land-based exercise versus no intervention, MD -1.2 VAS (95% CI -2.54 to 0.14).

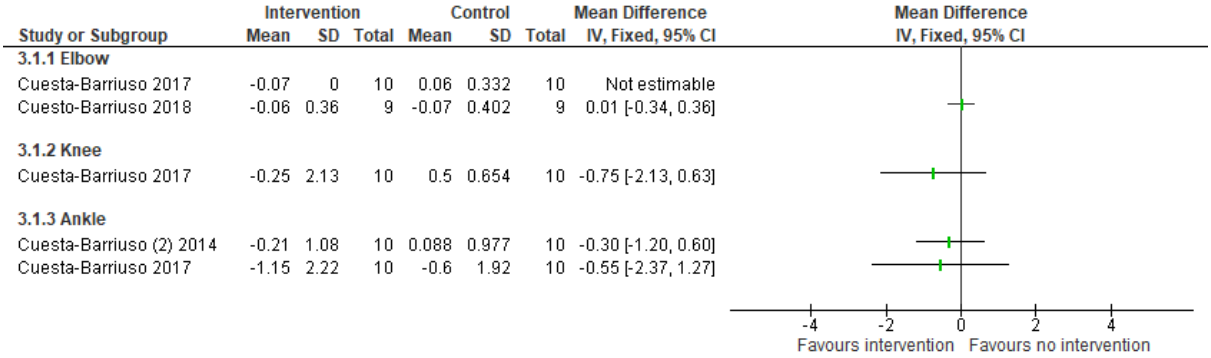
a. Hydrotherapy versus no intervention



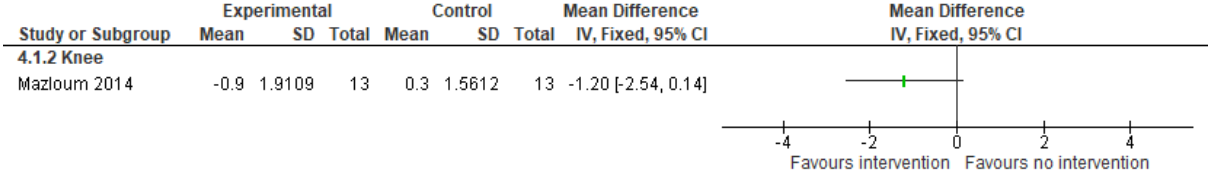
b. Manual therapy and exercises versus no intervention



c. Education and home exercise versus no intervention



d. Land based exercise versus no intervention



e. Fascial therapy versus no intervention

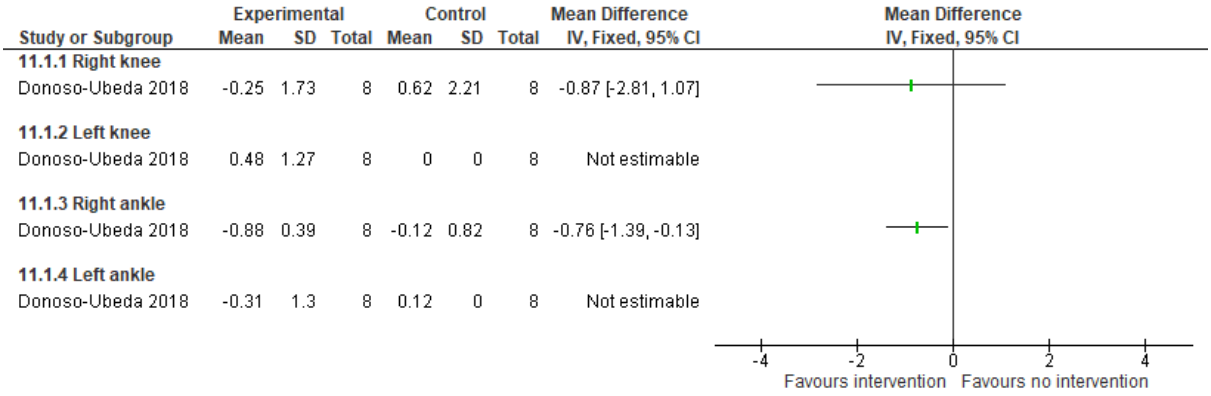


Figure 15: Forest plot comparison of physiotherapy intervention versus no intervention on pain

3.13.12 Secondary outcomes – Quality of life and Function

3.13.12.1 Quality of Life

One study, Cuesta-Barriuso (2017) (248), investigated the effects of patient education and home exercise programme (n=10) compared to no intervention (n=10) on patient reported quality of life. The interventions are described previously. It is not clear if there is any beneficial effect of the intervention on quality of life, MD QoL 18.50 (95% CI -2.25 to 39.25). (Figure 16)

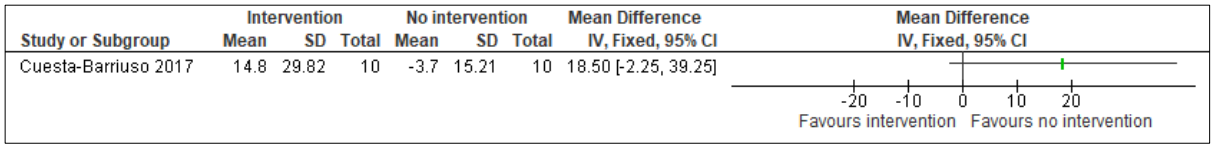


Figure 16: Forest plot for Physiotherapy intervention versus no intervention: Quality of Life

3.13.12.2 Function

None of the studies measured function as an outcome of intervention.

3.13.13 Physiotherapy intervention 'A' versus physiotherapy intervention 'B'

Seven studies were included in this comparison (231, 232, 242, 247, 250-252) and the forest plots are presented in Figure 17.

3.13.13.1 Primary Outcome - Pain

All seven trials included assessment of pain intensity using the visual analogue scale (VAS), with improvement in pain reported as a decrease in the VAS score. Five were conducted on adults over 18 years of age, and two on children between the ages of 9 and 13. All studies were RCT's and provided low to very low-quality evidence for the effect of physiotherapy interventions on the management of pain, quality of life and function.

One Cuesta-Barriuso study (2014) (232) investigated the effect of a joint mobilization and exercise intervention (n=5) versus a manual therapy and exercise intervention (n=4) on haemophilic ankle arthropathy pain. The study period lasted six weeks with participants receiving two one-hour sessions per week. The mobilisation intervention consisted of passive mobilisations to maximum range of movement in the ankles, resisted exercises for gastrocnemius, anterior/posterior tibialis, soleus and peroneal muscles and proprioception exercises. The manual therapy intervention consisted of ankle joint traction, active exercises using theraband, passive muscle stretching, proprioception exercise and joint stabilization exercises. Both arms used thermotherapy at the start and cryotherapy at the end of sessions. It is not clear if there is any beneficial effect of joint mobilization and exercise versus manual therapy and exercise for ankle pain, MD 0.4 VAS (95% CI -3.34 to 4.14).

Another Cuesta-Barriuso study (2014) (247) investigated the effect of manual therapy and exercise (n=11) or patient education and home exercise (n=10) versus no intervention (n=10) on pain intensity in haemophilic arthropathy of the ankle. The manual therapy and exercise arm consisted of thermotherapy to start, joint traction, passive gastrocnemius stretching and relaxation, isometric and resisted exercises and proprioception exercises, and cryotherapy to finish the session. The education intervention consisted of education on joint anatomy, joint bleeding and management, proprioception, and physical activity. The home exercise components were advised to be done twice a day and included range of motion, isometric and proprioceptive

exercises, as well as encouragement to do 20 minutes walking per day. It is not clear if there is any beneficial effect of manual therapy and exercise intervention over education and home exercises for ankle pain, MD 0.18 VAS (95% CI -1.38 to 1.75).

The Cuesta-Barriuso study in 2018 (242) investigated the effect of manual therapy and exercise (n=9) or patient education and home exercise (n=9) versus no intervention (n=9) on pain intensity in haemophilic arthropathy of the elbow. Both the manual therapy and education intervention arms were exactly the same as the previous study (described above) in 2014. It is not clear if there is any beneficial effect on elbow pain with manual therapy and exercise compared to patient education and home exercise, MD -0.31 VAS (95% CI -0.92 to 0.3).

The study by Mazloum et al (2014) (231) investigated the effect of hydrotherapy (n=14) or land based exercise (n=13) versus no intervention (n=13) on pain intensity in the knee of people with haemophilic arthropathy. The intervention has been described above. The results suggest that hydrotherapy has a more positive effect on knee pain than land-based exercise, MD -2.6 VAS (95% CI -4.02 to -1.18).

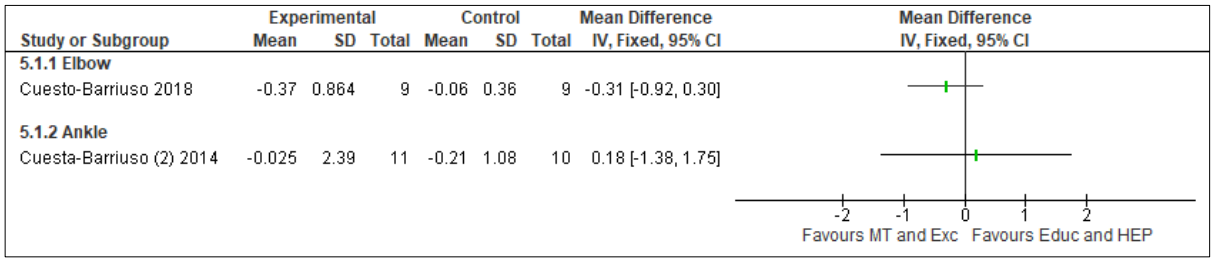
A study by Eid and Aly (2015) (250) investigated the effect of LASER and exercise (n=15) versus pulsed electromagnetic field (PEMF) treatment and exercise (n=15) on knee pain in children with haemophilia. The study period was over three months and both groups received 3 session per week of combined LASER or PEMF and exercise. The laser was applied to 5 points (40 secs each) at the knee including medial and lateral side of the patellar tendon, medial and lateral side of the knee adjacent to patella and over the suprapatellar pouch. The PEMF was applied to over both knees for 2 mins. As well as having a home exercise programme (not described), the exercise component was divided into 3 stages of acute haemarthrosis (cold packs and isometric exercises), subacute (isometric and isotonic exercises) and chronic arthropathy (hot packs, strengthening, stretching and proprioception exercises). It was unclear if this stratification applied to the whole group. The LASER and exercise arm had a more beneficial effect on knee pain compared to the PEMF and exercise arm, MD -1.07 VAS (95% CI -1.84 to -0.3).

Another study by El-Shamy and Abdelaal (2016) (251) also investigated the effect of LASER and exercise (n=15) compared to sham LASER and exercise (n=15) on knee pain

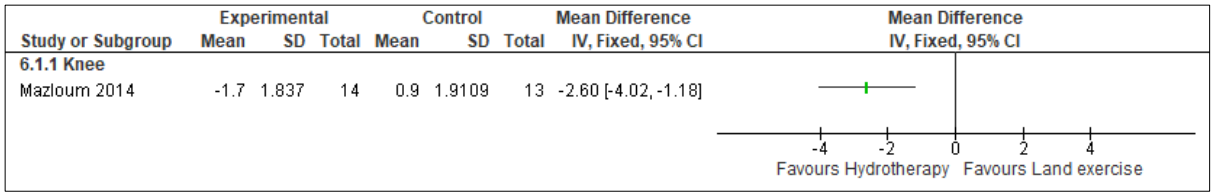
in children with haemophilia who had bilateral knee haemarthrosis. The study period was over 3 months whereby participants attended for one hour 3 days per week. The LASER application was over 10 points at the both the right and left knee for 8 mins for 36 sessions. The sham LASER group had the same procedure but with the machine not switched on. Both groups received a traditional physiotherapy programme that included hot packs, muscle stretching and strengthening, proprioception, balance, and gait training. The LASER and exercise group had a more positive effect on both left knee pain, MD -1.73 VAS (95% CI -2.23 to -1.23) and right knee pain, MD -1.61 VAS (95% CI -2.09 to -1.13) that the sham LASER arm.

A Study by Goto (2014) (252) investigated the effect of a home exercise programme (n=16) versus a home exercise programme that included a self-monitoring arm (n=16) on the knee and ankle pain in adults with haemophilia. With a study period of 8 weeks, both groups received education on a home exercise programme that consisted of guidance about strengthening knee extensors, static stretching for knee flexors, standing balance training and advice on promotion of physical activity to improve knee function. The programme was tailored, with the physiotherapist recommending the exercise most appropriate to each individual's physical condition, to be done 10 times per day. The self-monitoring arm were equipped with activity monitors that fed back to the researchers via the internet and mobile phone. When participants accessed the server to data input, feedback results appeared immediately in the form of graphs and tables. The exercise only arm could not view any of this information. It is not clear if there any beneficial effect on knee and ankle pain of a self-monitoring home exercise programme compared to an exercise programme alone, MD 0.62 VAS (95% CI -0.37 to 1.61).

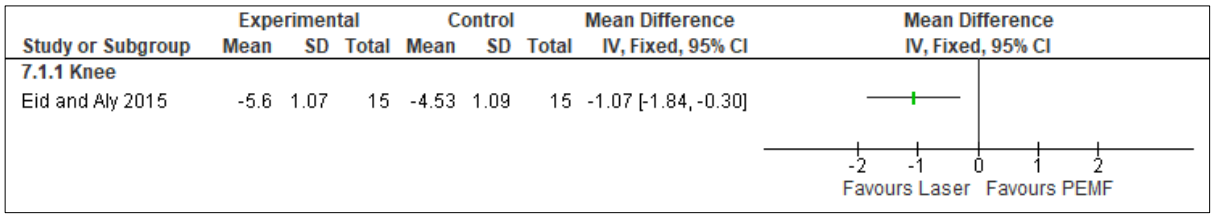
a. Manual therapy and exercise versus Education and home exercise



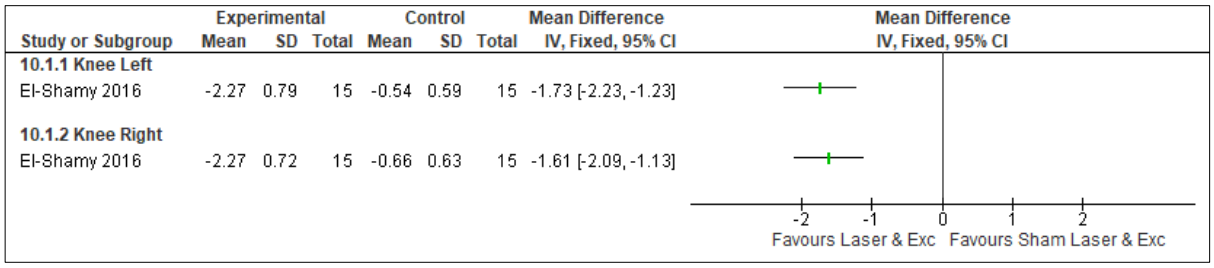
b. Hydrotherapy versus land exercise



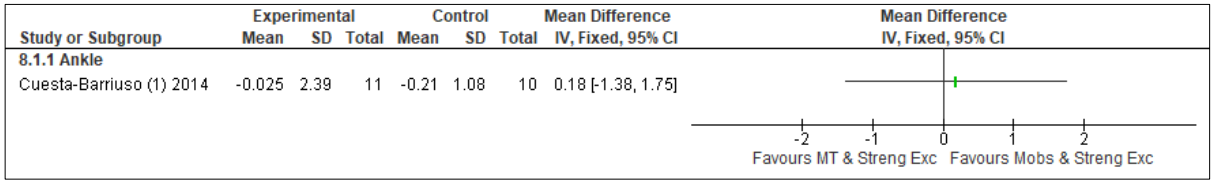
c. Laser versus PEMF



d. Laser and exercises versus placebo laser and exercise



e. Manual therapy and exercise versus mobilisations and exercise



f. Exercise and self-monitoring versus exercise alone

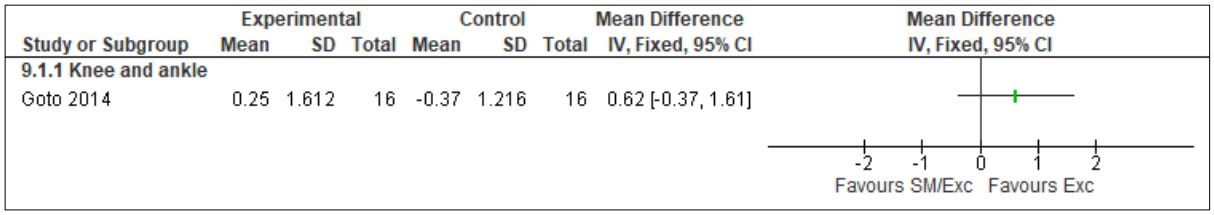


Figure 17: Forest plot comparison of physiotherapy intervention 'A' with intervention 'B' - Pain

3.13.14 Secondary outcomes – Quality of Life and Function

3.13.14.1 Quality of Life

Only one study, Cuesta-Barriuso study (2014) (232) investigated the effect of a joint mobilization and exercise intervention (n=5) versus a manual therapy and exercise intervention (n=4) on patient reported quality of life. The A-36 Hemofilia-QoL questionnaire was used. This is a 36-item questionnaire with a score range of 28-138 (higher score meaning better QoL). It is not clear if there is any beneficial effect on Quality of life from either intervention arm, MD -9.1 QoL (95% CI -47.2 to 29). (Figure 18)

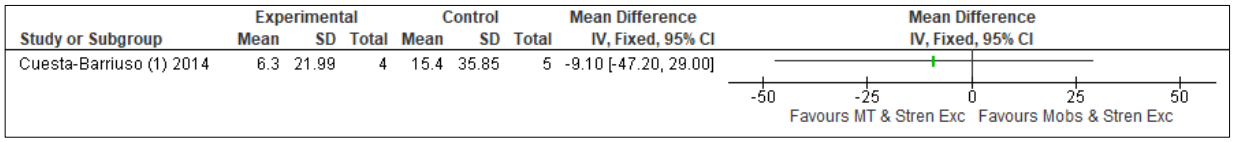


Figure 18: Forest plot comparison of physiotherapy intervention 'A' with intervention 'B' – Quality of Life

3.13.14.2 Function

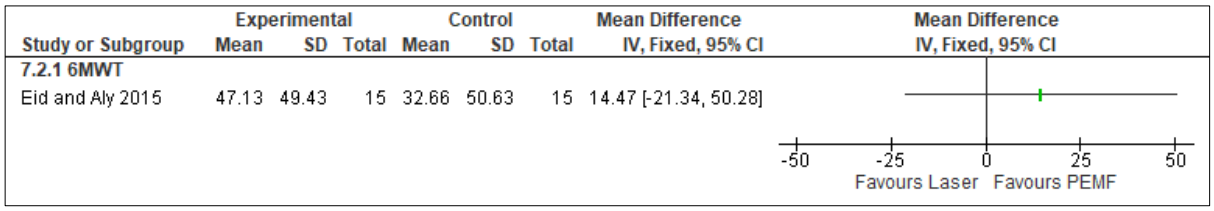
Three studies included a measure of function as an outcome measure of intervention and the results are presented in Figure 19.

Eid and Aly (2015) (250) investigated the effect of LASER and exercise (n=15) versus pulsed electromagnetic field (PEMF) treatment and exercise (n=15) on functional capability as measured by the 6-minute walk test (6MWT) in children with haemophilia. The interventions have been previously described. It is not clear if there is any beneficial effect on function with LASER and exercise compared to PEMF and exercise, MD 14.47 mins (95% CI -21.34 to 50.38).

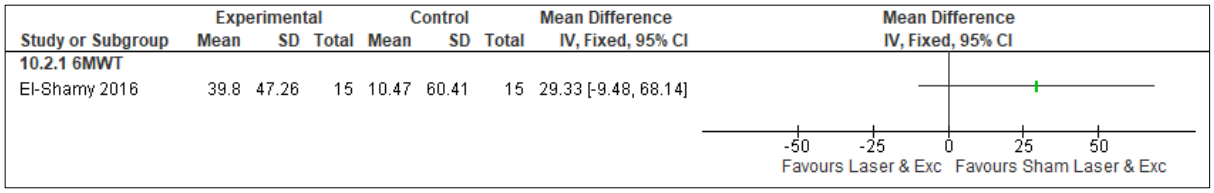
El-Shamy and Abdelaal (2016) (251) investigated the effect of LASER and exercise (n=15) compared to sham LASER and exercise (n=15) on functional ability in children with haemophilia also using the 6MWT. The interventions have been previously described. It is not clear if there is any beneficial effect on function with LASER and exercise versus sham LASER and exercise, MD 29.33 mins (95% CI -9.48 to 68.14).

Goto (2014) (252) investigated the effect of a home exercise programme (n=16) versus a home exercise programme that included a self-monitoring arm (n=16) on functional ability, using a modified reach test and 10 metre walk test (10MWT). The interventions have been previously described. It is not clear if there is any beneficial effect with self-monitoring and exercise versus exercise alone on modified reach test, MD 0.1 cm (95% CI -7.64 to 7.84) or on 6MWT, MD 0.4 secs (95% CI -0.84 to 1.64).

a. Laser versus PEMF



b. Laser and exercise versus placebo laser and exercise



c. Self-monitoring and exercise versus exercise alone

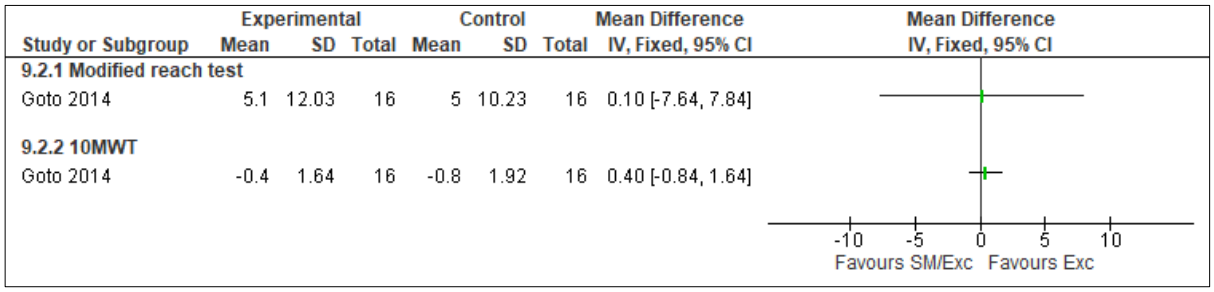


Figure 19: Forest plot comparison of physiotherapy intervention 'A' with intervention 'B' – Function

3.14 Discussion

3.14.1 Summary of evidence

This review presents the current evidence of studies evaluating a variety of physiotherapy approaches, which propose to have an effect on pain intensity, quality of life and functional ability in people with haemophilia. It demonstrates that currently there is low level evidence of effectiveness of physiotherapy interventions for any of these outcome measures.

The studies included in this review highlight the wide range of interventions being studied. Those interventions included joint manual therapy, passive joint mobilisations, exercise interventions, patient education, high intensity laser therapy (HILT), pulsed electromagnetic field treatment, hydrotherapy, and fascial release therapy. A significant number of them could be considered primarily passive in nature – that is, what is being 'done to' rather than with an individual to facilitate self-management strategies and activity.

Although this review only focussed on pain, function and QoL as outcomes, the included studies collected many varied outcome measures. These included safety of the intervention (defined by presence of bleeding), range of motion, swelling, laboratory blood sampling, gait analysis, radiological examination, illness behaviour, proprioception, balance, manually tested muscle strength, muscle/limb circumference, joint health examination/ assessment for arthropathy, self-efficacy and lumbar spine mobility. It is unclear in any study how these measures were chosen and if they have any relevance to PWH taking part in these studies. This is especially important given the wide-ranging implications that PWH with haemophilic arthropathy may have to live with.

The single approach of measuring only pain intensity with a VAS, highlights the lack of appreciation of the multi-dimensional aspects of pain, and a concerning lack of balance towards the complex outcome of pain that many PWH state is one of their major concerns (64). Three studies also collected multiple measures of the same outcome (such as VAS) per joint, which complicates the clinical relevance of study findings reported in this way (248) (253) (249). This is particularly relevant in PWH as many

present a multi-joint presentation across a wide age spectrum and variances in baseline musculoskeletal health, function, and well-being.

There have been previously completed systematic reviews that share some similarities to that conducted here. However, the quality of some of those reviews, as well as their results and recommendations, differ to those presented in this review.

The review by Gomis and colleagues (2009) aimed to evaluate exercise and sport in the treatment of PWH (234). Although it was described as a systematic review, it was a poor-quality review of published work, with a vague and broad inclusion criteria that included review studies, opinion pieces and case study series. It only provided a narrative description of work involving exercise and sport in PWH, without including analysis of the data from such papers, nor comparing results between studies.

Schäfer and colleagues (2016) in a review of physical exercise, pain and musculoskeletal function in PWH concluded that exercise promoted a reduction in pain, improved range of movement and strength in PWH (235). Although the authors utilised a double-blind reviewer approach with good data extraction described, they did not analyse the data any further than just presenting the included studies own results, thereby failing to interrogate this data further for effectiveness. Their review included three studies that were also reviewed in this study and concluded an opposite effect of bias in all three to those here (231, 232, 252). They also made reference in particular to Goto et al study (252) as to why they felt it may not have been as effective on pain by stating it may have been because thermotherapy was not included in the intervention. This perhaps highlights potential bias from the authors but also suggests a mechanistic approach to pain management with no acknowledgement of the multi-dimensional aspects of pain as a symptom in PWH.

A recent Cochrane Review on Exercise for haemophilia (236) was well conducted and included a broader range of outcomes in their analysis than in this review, although pain was analysed as a secondary outcome in many of their comparisons. Three studies were shared with this review and similarities in risk of bias were noted, as well as the review of the effectiveness of hydrotherapy as an intervention for pain management (231). Similar to the analysis here, they noted a major issue on the quality of how studies were conducted and reported, and encouraged caution with

results, highlighting that the safety of techniques described in reviewed studies remained unclear.

Two other systematic reviews looked specifically at physiotherapy in the management of haemophilic arthropathy. One focussed on the treatment of chronic haemophilic ankle arthropathy, and the review utilised a very broad inclusion criteria, which resulted in one paper that was a descriptive case series being included and labelled as a pre-test-post-test study (237). The focus of the analysis was on the physiotherapy intervention itself rather than comparing the effects of those interventions on specific identified outcome measures. This approach means that the recommendations from the review stating that there is a need for physiotherapy in ankle arthropathy management and which approaches are helpful must be interpreted with caution

The second review took a broader approach evaluating physiotherapy in the treatment of haemophilic arthropathy (254). The review methodology used only one reviewer which may lower the quality of the review and possibly raise the issue of potential bias. This is an important point as the author of the review was reviewing three of their own studies. As with the previous noted review, the focus on physiotherapy intervention type rather than the comparing effects of an intervention on specific outcomes means it is difficult to infer efficacy of any one specific intervention on measures such as pain and function. The authors stated that the studies included in their review represented a homogenous group, a statement to the contrary of the analysis from the review presented here. They also state that physiotherapy intervention in PWH and arthropathy is not complex, a statement that the researcher disagrees with.

3.15 Clinical Implications

This review highlights the unclear evidence of clinical effectiveness of many of the interventions discussed above. Trials evaluating physiotherapy can be considered a 'complex intervention' – that is, an intervention containing several interacting components targeting a range of behaviours (196). Haemophilia and its associated co-morbidities are a highly complex presentation and as a result, any physiotherapy intervention would be, by-proxy, a complex intervention. The studies included in this review do not appear to acknowledge or reflect this issue, nor present any discussion

about the approach required in a complex intervention. This may be a possible reason for the lack of effective results described here. Failing to account for the potential of complexity makes it difficult, therefore, to evaluate trials in their practical effectiveness, or by trying to identify what may be the active ingredients in how they may be exerting their proposed effects.

Both land-based exercises and hydrotherapy appear to have some positive effect on pain intensity, as does high intensity laser therapy combined with exercise. It is unclear if this is due to the focus of these interventions being mainly independent movement and activity along with skill acquisition and self-efficacy. Although hydrotherapy appears safe and potentially effective for pain management, further well conducted trials are necessary.

Education showed little positive effect when used in conjunction with exercise, or manual therapy. It is not clear from any of the studies using it how the teaching curriculum was developed. If it was a patriarchal approach to education, without participant involvement in identifying issues and needs, then it may lack relevance to the participants. Health education is complex and requires adequate definition as to whether it is targeting health literacy (which is dependent on fundamental literacy and associated cognitive development), health promotion or health behaviours. Including health education without consideration for potential behaviour change models of action, limits evaluation of how any education provision may be having its effect (255). This highlights the need for continued work on the involvement of PWH in trial design ensuring relevant interventions and appropriate outcomes on what matter most to them.

No study defined pain as a specific inclusion criteria, thereby all studies appear to implicitly assume that pain is present in all joints in all participants as part of the study. However, on closer inspection of the data, this does not appear to be the case. Such poor study design means that trials included a measure of pain, even though some participants recorded it as zero at the start of the intervention, therefore leaving little room for evaluating meaningful change following the intervention.

Across many of the studies, the small differences in pre and post intervention pain VAS highlights only a small intervention effect. It is unclear if this is due to a low pain VAS

report pre-intervention (i.e., they had less/minimal pain upon starting the intervention, which was true for some participants in the reviewed studies) or a lack of effect of the intervention as it was not targeting that individual's main issue. No study made any attempt to contextualise the multi-dimensional aspects of pain and how, if present, it could affect participation in trial activities, as well as outcomes. Such omissions mean that it remains unclear if the physiotherapy interventions described in these studies could be used effectively in pain management approaches for PWH.

Many of the studies also recorded pain measures from multiple joints. This appears to be because many of the participants had a wide range and number of joints affected by haemophilic arthropathy – and so the authors included a pain measure from all the joints in all the participants. This approach may make it difficult to evaluate potentially successful components of the intervention, especially if some participants had more or less or no pain in other joints being measured. It is worth considering the negative value of joint specific pain assessment when so many joints are involved and highlights the need for strong, well-defined study aims, objectives and outcomes to be measured when such individuals are included in trials.

Only two studies included quality of life assessment (232, 248) and three included an assessment of function (250, 252, 253). The minimal evaluation of psychological and social aspects of well-being alongside pain or basic joint function (such as range of movement) makes no clear distinction of what the interventions mean to the individual taking part. Such limited data gives no personal context for change as a result of an intervention – and remains that most of the outcome measures collected were primarily about body structure and function and less about person-specific activities, function, or participation in daily life.

3.16 Limitations of included studies

Overall, the methodology and reporting quality of many of the trials included in this review was poor. Proceeding to meta-analysis was not feasible due to the high degree of heterogeneity with interventions. This included the wide age range of participants, the type and number of joints being evaluated, mixed diagnosis relating to the severity of haemophilia, wide range of time frames for interventions being conducted and a wide range of patient reported outcome measures. Participant numbers were low for

all included trials, and four of the trials were randomised pilot studies (232, 242, 247, 249).

No trial included only people with severe haemophilia. This is an important factor in considering the implications of potential effects of physiotherapy interventions in PWH. For many of those born in an era with little access to factor concentrate, or those in developing nations where the health system cannot support access to rudimentary amounts of factor concentrate replacement – severe haemophilia remains a diagnosis most likely to result in multi-joint arthropathy, and potentially pain and functional issues. This makes it difficult to extrapolate from the current data to those people with severe haemophilia.

Pain was not a separate inclusion criteria for any of the nine trials included in this review. An implicit assumption appears to have been made by all the authors, that having a diagnosis of haemophilia and/or haemophilic arthropathy and/or synovitis in any combination would always equate to having pain. No distinction is made of the nature of the pain, i.e., acute or chronic, nor if the presence of pain was actually of any concern to those individuals taking part.

Two of the nine studies failed to describe in their aims any clear participant relevant outcomes, instead the aim was a test of the intervention itself for safety (242, 249). However, both studies went on to collect large numbers of outcomes that appear to defend the therapeutic approach. No feedback from participants was included in any study, making it difficult to fully appreciate any value such interventions may have had.

On closer review of four studies, it would appear that the same cohort of participants may have been used (232, 242, 247, 248). Although many years apart in publication date, the ethical approval information was the same for three, as was the small geographical location of the included participants in all four studies (232, 242, 247). It is unclear if there were three separate trials, or if only one data collection happened and resulted in a 'salami production' of data and papers. If it were three separate trials, then given the potential for the same participants being included, the authors did not acknowledge or take account of the potential for the learned effect of the intervention being studied. This could have significant implications for results, and as such introduces further unknown bias into interpretation of the resulting data.

None of the studies appear to have involved PWH in the design of their studies, nor evaluated any qualitative measure of participation in such trials. As a rare disease, many PWH can be considered experts not just in their condition, but also in potentially identifying what matters to them in respect of rehabilitation interventions. It is imperative that PWH who report chronic, problematic pain are included in trial design.

3.17 Strengths and limitations of this review

A strength of this review is the process of using two reviewers throughout the process. Inclusion/exclusion of potential reviews was completed blindly, and agreement reached with discussion afterwards. Risk of bias and GRADE assessments were also conducted blindly to reduce bias. Unlike many of the previous similar systematic reviews, data was analysed to produce confidence intervals (CI's) and mean difference (MD) figures, allowing a good visual representation of effectiveness.

A limitation of this review has been the inability to proceed towards completing a meta-analysis of the data from any of the included studies. This precludes any clear recommendations for the use of physiotherapy interventions in the management of pain in haemophilia. Although a diagnosis of haemophilia could be perceived as a homogenous group, the significant co-morbidities associated with having a diagnosis of severe haemophilia A or B over that of mild haemophilia mean that in musculoskeletal research there should be clearer and more precise inclusion/exclusion criteria for within group comparison.

This study was published in April 2020. Since then, there have been some further studies published that would fulfil the inclusion criteria for this review, however the review itself was not updated for inclusion in this chapter. There is no clear guidance on when to update a systematic review. Recent consensus guidance suggests that an update should only be considered if new studies or data is expected to change the findings or credibility of the existing findings so as to justify the effort and time required in the updating process (256). A rerun of the original search in May 2022 found a further six studies fitting the criteria. The studies evaluated pain intensity (VAS or Numerical scale) after myofascial release at the elbow (257), manual therapy and stretching at the knee (258), manual therapy and strengthening exercise for the elbow(259), manual therapy and exercise for joints of the lower limb (260) and

combined cognitive behavioural therapy and whole body exercise (141). One other study investigating myofascial release at the ankle (261) appeared to be an extension of a similar study by the same authors included in this review (249). Only two included a quality of life assessment (141, 259), or assessment of function (259, 260). The heterogenous nature of the interventions with regard to technique and body part treated is similar to the studies included in this systematic review. Therefore, the need to update the current review was not felt to be justified, however it is hoped that an update will be indicated in the future as more studies become available.

3.18 Implications for Research

The results from this review highlight issues with the current state of research associated with physiotherapy for pain management in haemophilia.

It is clear that better designed trials, with user involvement in their design is crucial. Better defined inclusion criteria specific to severity of disease, as well as pain as a self-reported symptom are needed to better assess efficacy of any interventions. It must be defined from service users themselves what information about their disease process they want to know more about, rather than a catch-all approach of broad, medically orientated, and paternalistic education.

The physiotherapy interventions themselves need to be more active in their approach, to engage people living with these conditions and to foster self-efficacy and better control of their symptoms.

The current use of only VAS in measuring pain intensity requires further scrutiny. Pain as a multi-modal, personal, lived experience is poorly evaluated measuring intensity alone. Further trials need to focus on what living with long standing pain means to the individual and how future interventions may be designed to best evaluate changes to function and physical, social, psychological well-being.

Reporting of trials needs to be better so that this emerging body of research can be effectively collated and compared, to permit development of effective interventions for pain in haemophilia.

3.19 Conclusion

This systematic review highlights low to very low-quality evidence for the use of physiotherapy interventions for pain management in people with haemophilia.

Hydrotherapy and land-based exercise appears to have some positive effect on knee pain in adults with haemophilia but care must be taken with this recommendation due to poor quality reporting and high risk of bias in this trial. It is not possible to make recommendations on any other physiotherapy intervention in the management of pain in haemophilia due to unclear beneficial effect and poor-quality trial design.

Further research needs to employ improved trial design and methodology along with better reporting of results. More research needs to address the underpinnings of what matters most to people with severe haemophilia who live with chronic pain, along with what an optimal rehabilitation intervention could look like for them. Future studies need to also consider what makes an intervention work, its effective components and how all aspects of trial design can be evaluated both by those designing it, but also by those taking part in it.

As well as reporting a low quality of evidence for physiotherapy interventions, this chapter has also highlighted the limitations in current studies when considering the lived experience of pain for PWH. The next chapter present the findings of a qualitative study in PWH and healthcare professionals that investigated their views, experiences and beliefs of pain and its management.

Chapter 4 - Qualitative study

This chapter describes the methods and findings of a qualitative study conducted with PWH and healthcare professionals that aimed to investigate their experiences, views and beliefs of pain and its management. The analytic method of reflexive thematic analysis is described and includes in-depth reflexive evaluation of the researchers involvement and how this impacts on the trustworthiness of the findings. The findings of this study were successfully submitted for publication in two separate but complementary manuscripts in the same edition of Disability and Rehabilitation journal (262, 263). The text in this chapter, therefore, is similar to what was published (Appendix K). Although in this chapter a cohesive description of the whole 'story' is presented, with additional detail not found in the publications.

4.1 Background

Bleeding and its management has been traditionally viewed within a model of biomedical intervention. Whilst this is appropriate within an acute bleed treatment episode or when engaging PWH in prophylaxis regimes to prevent bleeding, it struggles as a model of care in recognising the many competing experiences and influences which impact how an individual lives with their haemophilia. Pain associated with haemophilic arthropathy interferes with daily activity, mobility, work, and employment prospects (70, 110). PWH who have co-existing acute and chronic pain report a significant negative impact to their quality of life (114), which is made worse with multiple affected joints (264). Recent UK NICE guidelines for chronic pain management encourage a more person centred approach (101) but there are limited accounts of the subjective exploration and attempts to understand the pain experiences of PWH. Knowledge and understanding of the life experiences of PWH in relation to haemophilia in their family, experiences of treatment and their own cultural and medico-social experiences may help enhance and inform approaches to pain management in the clinical context.

Despite the scale of the problem, there remains little in the way of published guidance for effective management of chronic arthropathic joint pain in PWH. Between 21-50% of PWH feel that their pain is poorly managed by healthcare teams (66, 69) and this

likely accounts, in part, for the wide range of strategies for pain management reported by PWH. Surveys in PWH have highlighted additional clotting factor treatment, opioids and non-steroidal anti-inflammatories, as well as rest, ice, compression and elevation remain the most widely used methods for both acute and chronic pain (60, 121), with other approaches including prayer, relaxation, deep breathing and swimming also being used (61, 115). Whilst some have recently stated the importance of multi-professional expertise for pain management in PWH (265), psychology, physiotherapy or exercise based strategies are seldom reported as being used by PWH (115, 128).

The evidence base for effective and cohesive pain management approaches in PWH is lacking. NSAID's and in particular COX-2 inhibitors, have shown more positive effect on reducing pain intensity than acetaminophen in those PWH who have haemophilic arthropathy (134, 266), but worries remain about potential bleed risk if used for an extended time (133). A psychologically based approach using an educational DVD that sought to influence self-efficacy in managing pain demonstrated shifting participants from a pre-contemplative to contemplative state of readiness to change (267). Another small pilot study using hypnosis showed some positive, but not significant improvement effect on pain interference and quality of life (139). Whilst exercise in general appears safe to do with PWH (236), the findings of the systematic review in Chapter 3 found that there is low level evidence of effectiveness of many physiotherapy interventions (exercise, manual therapy, electrotherapeutic agents) on pain and functional outcomes (226). A recent study implementing a combined intensive physiotherapy/ occupational therapy intervention of strength and balance exercises, group work and education and rehabilitative approaches to activities of daily living was unable to show any significant improvements in pain or quality of life (268). Whilst some authors have identified fear of bleeding and further pain as barriers to being more active with haemophilia (269), there remains relatively little understanding of the lived experience of PWH and how they manage their pain, as well as the experiences of the healthcare professionals who look after them.

To date no-one has asked people with this condition if they would want to participate in, or perceive a need for, exercise-based rehabilitation for pain management. Another unknown for clinicians is whether PWH with chronic pain would even want to

participate in such activity and what their fears and motivations around exercising may be.

4.2 Study aim

The aim of this study was to explore the views and beliefs of PWH and healthcare professionals on the experience of pain and pain management strategies, as well as their views and opinions on rehabilitation for chronic pain. This in turn reflects the need to provide context for the telerehabilitation study that was subsequently developed.

4.3 Methods

4.3.1 Study design

As this was an explorative study seeking to better understand the phenomenon of pain in PWH, and the views and beliefs around pain and its management from both PWH and haemophilia healthcare professionals, a qualitative approach using focus groups and semi-structured interviews was used. Focus groups brings together a group of people in order to discuss and share their own views and experiences around a particular topic, whilst semi-structured interviews allow participants to speak freely and provide their own views around the topic at hand (270).

There is an urgency in the need to attempt to contextualise healthcare approaches to pain with the experience of the PWH receiving that care. In seeking to better understand each participants own subjective reality about pain management and their views and beliefs about exercise, a philosophical position of constructivism was taken. As no predetermined theories or frameworks were used, an inductive approach to analysis was used.

4.3.2 Reflexivity

Rigour and reflexivity throughout the study were maintained with regular research team meetings, a clinical supervisor (KK) being present at the focus groups, and analysis and review of field notes and reflections. Analysis of data was discussed with the research team (one female nurse researcher, one female haematologist, two male academics and one male person with haemophilia) and themes were discussed and modified as necessary.

4.3.3 Recruitment

Participants were purposively selected from southeast and northwest England in order to achieve a variety of views and experiences. The study was advertised on social media and on posters that were displayed in haemophilia centres (Appendix E). For those people with haemophilia, inclusion criteria were a diagnosis of severe haemophilia A or B, who self-identified as having persistent pain associated with their haemophilia and haemophilic arthropathy, aged 18 or over and with an absence of any other condition that would be responsible for the presence of persisting musculoskeletal pain. A participant information sheet was given to those who expressed an interest. (Appendix F)

As the healthcare professionals most likely to have first-hand experience of pain in PWH, an invitation to participate email was sent via the professional clinical interest groups of haematologists, physiotherapists, nurses, and psychological professionals working in haemophilia in the UK. Inclusion criteria for the healthcare professionals was the requirement to have experience in working clinically with PWH in adult haemophilia centres.

All participants (PWH and healthcare professionals) had to be able to communicate in spoken English. Those interested were encouraged to contact the researcher by phone or email to initiate further discussions to clarify any queries as well as check inclusion criteria.

4.3.4 Setting/ location

Due to the musculoskeletal manifestations of haemophilia, it was anticipated that potential participants may have significant multi-joint arthropathy and so locations for the focus groups were chosen for accessibility, availability of car parking and access to good public transport links. Prior to both meetings, all participants were sent detailed travel information about the venues, parking, and transport links. All participants were advised that travel/parking expenses incurred would be reimbursed following the meeting.

Interviews and focus groups were conducted between June 2019 and March 2020. Two face-to-face focus groups were held for PWH in south-east and north-west England. Due to the Covid-19 pandemic restrictions, interviews with PWH were

conducted over the telephone at a mutually convenient time agreed in advance with participants.

Although a focus group was planned for healthcare professionals, meeting logistics agreeable to all who expressed an interest were not forthcoming, so it was decided to proceed with semi-structured face to face interviews instead. Interviews were arranged at times and places most suitable to the interviewee.

4.3.5 Focus group and interview procedure

Written informed consent was taken on arrival at the focus groups and face to face interviews and over email on the day of the telephone interviews (Appendix G). The study was approved by the St. Georges University of London Research Ethics committee (reference no. 2018.0309) (Appendix D).

Topic guides were used for the PWH focus group, PWH interviews and healthcare professional interviews based on the overall aims of the study (Appendices H and I). These were developed in partnership with CS (PWH in research management group) and were informed by the current research literature in the area, clinical experience, and the research question at hand. Questions were open ended allowing naturalistic responses. Probing questions and prompts were also used in the groups and interviews to gain deeper understanding of experiences and views being discussed. The approach was flexible enough to enable and engage with topics and discussions that were introduced by participants as relevant to them. Two moderators were present at the focus groups. The researcher led the group discussions and a second clinical supervisor (KK) provided support in participant observation, making field notes, and aiding those noted to be quieter to be drawn into conversations.

Both focus groups and all the interviews were digitally audio recorded and transcribed verbatim.

4.3.6 Analysis

NVivo 12 Pro® was used was used to manage the dataset (transcripts and field notes). This programme was used only to aid in the storage and organisation of the data, not to generate codes or themes or interpret the data. Use of technology such as this is acceptable in reflexive thematic analysis so long as the researcher is reflexively aware of their role in data interpretation and adequately reports that process (271).

Data was analysed using a reflexive thematic analysis approach following Braun and Clarke's 6-phase process (272, 273). Broadly, thematic analysis is an approach that seeks to identify and analyse patterns in data. It is a shared approach across other analytic methods such as interpretative phenomenological analysis and grounded theory. However, specific methodology pertaining to developing code and themes structures heavily influence how data are managed and analysed. Different methodological approaches to coding are viewed on a continuum, strongly influenced by the researcher's ontological and epistemological standpoints. (Table 5)

Table 5: Overview of coding approaches in thematic analysis (adapted from Braun and Clarke 2021) (274)

Coding reliability approach	Reflexive approach	Codebook approach
Early development of themes Coding is a process of identifying evidence for themes Researcher subjectivity conceptualised as bias – therefore, multiple coders used Final coding is done through consensus	Later theme development Themes developed from codes Coding is unstructured and organic Conceptualised as pattern of shared meaning (underpinned by central organising concept) High degree of analytical/interpretative work by researcher Themes generated by researcher through data engagement – they are part of the process	Used to chart and map developing analysis, not to determine validity and accuracy of coding Combines qualitative values of reflexive approach with more structured approach to coding/early theme development in coding reliability

Reflexive thematic analysis however, acknowledges the importance of the researcher subjectively as an analytic resource as well as a resource for knowledge production (274). This interpretivist approach views the researcher as never being truly separate from their own values and beliefs (275) and so places the researchers ontological view as one that recognises multiple realities (relativist) within a subjective epistemology.

An inductive approach to reflexive thematic analysis allows the views of participants to build up to inform theory and interpretation.

The data were analysed using reflexive thematic analysis following the six-phase process described by Braun and Clarke (Table 6) (271-273).

Table 6: The six phases of reflexive thematic analysis

Phase 1: Familiarisation with the dataset
- Familiarity with dataset through immersion - Listening to audio of transcripts - Reading/re-reading data - Making brief notes/ analytical insights
Phase 2: Coding
- Work systematically through dataset - Identify potentially interesting/ relevant/ meaningful segments – apply code labels - Codes – specific and detailed – capturing single meaning/concepts - Coding at range of levels – semantic to latent - Code entire dataset - Collate code labels, compile relevant segments of data for each code
Phase 3: Generating initial themes
- Identify shared patterns of meaning across dataset - Compile clusters of codes that share core idea/ concept - Active theme development – defining broader, shared meaning – candidate themes - Collate all coded data relevant to candidate themes
Phase 4: Developing and reviewing themes
- Assess fit of initial candidate themes to the data - Check themes make sense in relation to coded extracts and full dataset - Do themes highlight most important patterns across dataset - Do themes relate to the research question - Candidate themes may be collapsed, split, retained, discarded - Consider relationship between themes and existing knowledge/ practice
Phase 5: Refining, defining and naming themes
- Fine tune the analysis - Each theme should be clearly demarcated, built around strong core concept - What story does the theme tell? - Concise and informative name for each theme
Phase 6: Writing up
- Integral phase of analytic process for thematic analysis - Writing often starts from Phase 3 - Aim is to weave together analytic narrative and compelling data extracts

Transcripts were initially read alongside the recording of the interview, first to check for accuracy of transcription and then again as a way to begin immersion in the data. Coding within reflexive TA is not a process for finding pre-conceptualised themes, but instead is integral to theme development (274). The researcher led the analytic process of coding and theme development with coding being initially semantic (surface meaning) then progressing through to latent interpretations of data and codes. This was a fluid process with data from both PWH and healthcare professionals being coded as one data set leading to initial theme development.

In the initial stages, coding was completed solely on NVivo. However, theme development at this stage was somewhat problematic as it was proving difficult to envision and encapsulate 'a story' within the data in this format. Therefore, the researcher took the decision to print the participant responses that was saved within each code tree in NVivo. Using this approach made it visually easier to think through how similar coded sections were fitting together, and in developing more coherent early candidate themes. Another paper-based method using post-it notes was also used to further distil more discrete sections of coded data. This aided the formalisation of more robust themes, and the overall theme structure for the whole dataset. Details of this approach to theme development cand be found in Appendix J.

The concept of data saturation was not used here as an end point to coding and theme development. Instead, and in keeping with a reflexive thematic analysis approach, codes and themes were not identified a-priori to data analysis. In a critical review of data saturation, Braun and Clark state that meaning in data resides at the intersection of the data and the researchers contextual and theoretically embedded interpretative practices i.e. that meaning requires interpretation (273). The inductive approach used here represents situated and contextual engagement and interpretation of data by the researcher as a highly experienced clinician as opposed to consensus as used in a coding reliability approach between coders.

Initial interpretations of codes, broad theme development and thoughts about the data's story were discussed together by the researcher and a clinical supervisor (KK). As theme development became more solid, the wider research team discussed the findings leading to further refinement and analysis with codes being merged, removed, expanded, and renamed as the data was further interrogated. This fluid, dynamic and

recursive approach is key to the analytical approach advocated in reflexive thematic analysis.

4.4 Results

A total of 14 people with haemophilia and six healthcare professionals volunteered to take part in this study. Eleven PWH attended two focus groups and 3 were interviewed over the telephone. The healthcare professionals were all interviewed face to face. There were approximately 15 hours of recorded interviews transcribed.

The demographic information for the participants with haemophilia (Table 7) and healthcare professionals (Table 8) is presented below. Pseudonyms are included for use in the narrative that follows.

Table 7: Anonymised Participant Demographics and Pseudonyms – people with haemophilia

	Pseudonym	Age	Diagnosis	UK/Non-UK Born	Employment	Prophylaxis
1	Tony	55	SHA	Non	Yes	Yes
2	Adam	28	SHA	UK	No	Yes
3	John	42	SHA	UK	Yes	Yes
4	Jack	57	SHA	UK	No	Yes
5	Greg	39	SHB	UK	Yes	Yes
6	Will	52	SHA	Non	No	Yes
7	Ivan	73	SHB	UK	Retired	Yes
8	Alex	58	SHA	UK	Retired	Yes
9	Owen	52	SHA	Non	Yes	Yes
10	Andy	40	SHA	Non	Yes	Yes
11	Hugh	65	SHA inhib	UK	Retired	Yes
12	Sean	23	SHA	Non	Student	Yes
13	Leon	28	SHB inhib	UK	Yes	Yes
14	Nick	30	SHA	UK	Yes	Yes

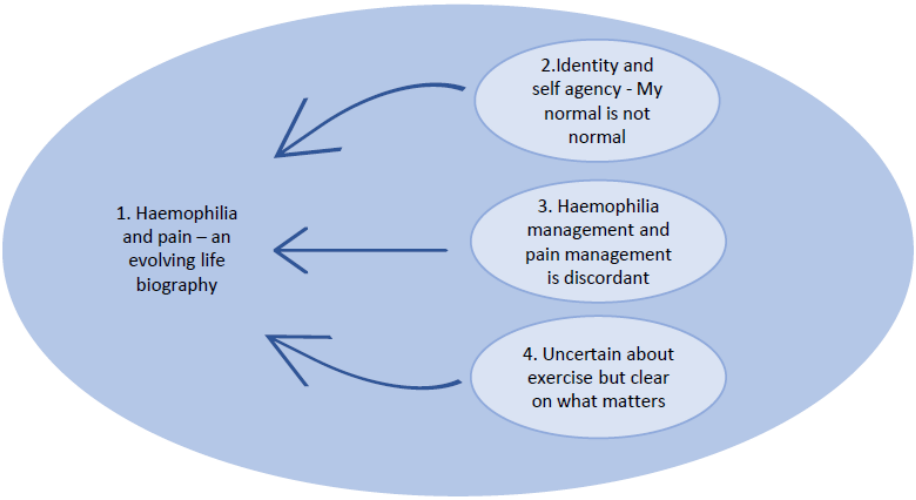
Key: SHA: Severe Haemophilia A; SHB: Severe Haemophilia B; Inhib: Inhibitor to factor VIII or IX

Table 8: Anonymised Participant Demographics and Pseudonyms – Healthcare professionals

	Pseudonym	Profession	Years working in haemophilia
1	Emma	Clinical Nurse Specialist	14
2	Kate	Physiotherapist	13
3	Neil	Haematologist	15
4	Mary	Psychology Professional	20
5	Ruth	Haematologist	9
6	Rose	Physiotherapist	4

Four themes were conceptualised from the data and are presented in Figure 20.

1. Haemophilia and pain – an evolving life biography
2. Identity and self-agency - My normal is not normal
3. Haemophilia management and pain management is discordant
4. Uncertain about exercise but clear on what matters.



THEME	Haemophilia and Pain – an evolving life biography	Identity and Self agency – My normal is not normal	Haemophilia management and pain management is discordant	Uncertain about exercise but clear on what matters
Sub-themes	- Historical narrative of haemophilia - Haemophilia, pain and the family - Fear, consequence and adaptation	- Physicality and ableism - Identity within and despite haemophilia	- Experience, knowledge and understanding of pain - Healthcare provision and approaches to care - Trust in healthcare professionals - Strategies for pain management	- Barriers, enablers and the need for more proof - Practicalities, logistics and outcomes

Figure 20: Map of key themes and subthemes

4.4.1 Theme 1: Haemophilia and pain – an evolving life biography

Here the medical, historical, and social evolution of life with haemophilia is explored, particularly relating to living with a rare disease and all the issues that come from it, of which pain is a key component. This theme can be considered an overarching theme to the whole dataset as the remaining themes all relate back to it.

4.4.1.1 Subtheme: The historical narrative of haemophilia

For men aged in their 50's and 60's, early life experience with medical care of haemophilia is primarily reflective on a lack of any medical treatment and limited awareness of haemophilia. Significant periods of hospitalised immobilisation were normal, and invariably ended up provoking further bleeding. In early years, a lack of treatment and expertise from both parents and the medical profession meant that being cared for was viewed as '*damage limitation'(Hugh, 65)*. Medical advice in the absence of effective haemophilia treatment is recalled by participants as extremely varied and with limited success. However, for almost all older participants, 'excruciating' pain from bleeding was a repeated and common experience of growing up with haemophilia-

> *"I remember one incident where I was on admission and I had multiple anal inserts, and unfortunately once you get one in they can't give you another for a couple more hours. At the end of the day, they had to resort to morphine shots to calm me down, and even that couldn't keep me calm for, like, 15 to 20 minutes before the pain starts to shoot through the roof again."(Andy, 40)*

Local medical care, and inadequate or potentially dangerous interventions for pain relief were the norm until development of, and access to, effective medical treatment revolutionised bleed management. As cryoprecipitate was discovered and replaced whole blood infusions the benefits on pain and bleeding were clear to see:

> "*This must have been in the early '60s, I think – they gave me one of the first experimental doses of the factor IX concentrate, and that worked. And I thought, "WOW!" ... Because that fairly quickly stopped the bleed and the pain went down"(Ivan, 73)*

As treatment advanced from hospital-based cryoprecipitate to factor concentrates administered independently at home, people with haemophilia began to see positive enhancements to their life and activity. The relationship between the symptom of pain and the possibility of it being a bleed is complex and has evolved over time and with age, experience, treatment improvements and availability. However, the advent of

effective prophylaxis and diminishing spontaneous bleeds means PWH are now having to challenge their own internal reasoning and decision making processes on using pain as a marker for bleeding-

> *"I suppose you don't really know the difference, because you would always associate a joint pain with a bleed" (Adam, 28)*

4.4.1.2 Subtheme: Haemophilia, pain, and the family

The diagnosis of haemophilia within a family was for some a catastrophic disruption to life for parents. A child with haemophilia meant that they were required to blindly navigate imperfect medical care as well as trying to provide the best parental care and protection they could, at a time when knowledge and medical provision were scarce -

> *"… diagnosed at six weeks old – I think, from memory – it came as a complete shock to my parents. They'd never heard of haemophilia or how to cope with it, or how to manage me. I was their son. I was in incredible pain a lot of the time." (Ivan, 73)*

Early presentations of bleeding and pain were often underplayed by doctors at the time. Many recalled detailed episodes of medical interactions, whereby their pain as a symptom was ignored and underplayed by a medical professional, to the point of making parents feel inadequate or time-wasting. Living with haemophilia and the bleeding episodes was disruptive to family life, familial roles, and relationships. The child with haemophilia brought with it responsibilities and need for management that was more than what would be seen normally within other families. Relationships were strained and difficult with bleeding episodes. Fear and worry of having to tell a parent of a bleed resulted in many hours of no treatment due to fear of an angry response-

> *"And my dad was like really strict, so what I'd do is, if I hurt myself, I'd try and treat myself, like get… like try and… "Oh God, I've got to tell him, I've got to tell him." And then the ambulance would come, like half eleven at night, and I'd make it worse, and I'd have to be in hospital."(Jack, 57)*

The fears and risks around treatment associated with the infected blood issues of the early 1980's added further unimaginable responsibility to maternal decision making to treat bleeding, with significant consequences now in adult life as noted by healthcare professionals' -

> *"I've got a… he's moderate or severe, who only ever used… had targeted factor because his mum always worried about factor safety back in the '70s, '80s and*

'90s. So, he had been… he had grown up by avoiding activity as a way of managing bleeds, but now it's become avoidance to manage pain."(Rose, PT)

Pain associated with their haemophilia was an ever present and normalised feature within the family unit whilst growing up. How participants experienced, reported, and behaved with pain has evolved into their adult lives, with pain continuing to be a feature with them in their families now. Pain is viewed as a personal experience and not one to be shared or discussed with their partners:

"I discuss things with her, but I keep my pain to myself… that's not their issue or their problem. And they can't do anything about it either, can they?... There's nothing wrong with that. So, I just keep that to myself. It's no one else's problem but mine."(John, 42)

4.4.1.3 Subtheme: Fear, consequence, and adaptation

The fear that a sensation of pain may be a sign of possible bleeding permeates all cognitive processes, behaviours, and activity choices in the lives of men with severe haemophilia. The fear of bleeding appears to be worse than the fear of pain itself.

"The last thing you want is a bleed – that's the thing to avoid." (Tony, 55)

Whilst pain is unpleasant, it is an experience that is accepted as almost always being present and is to a degree, accommodated and moderated. Bleeding, although intermittent, is unpredictable and viewed as having greater consequences on immediate physical and social interactions, as well as for the future-

"I'm just sort of thinking… pain is like half an inch away from… not a bleed, but disaster. You know, because you might not just have a bleed – like a bad knee, a bad arm or something. I've been hospitalised with a psoas bleed and I was lucky to stand up straight after that."(Hugh, 65)

The fear of bleeding appears to dissipate to some degree when taking prophylaxis. Fear and anxiety as a response is still manifest, but more in relation to the consequences of a lifetime of haemophilia on their physical, social, and psychological wellbeing. Worry about bleeding merges with the stress of monitoring the state of their joint on a daily basis:

"…with the joint pain for me: there's a degree of unpredictability. Some days you can just push through and yes, you may be sore the next morning, but you will be okay. And other days, you're going to be in a lot of pain that night." (Will, 52)

Haemophilia and its physical side effects is viewed as something that prevents an acceptable, predictable continuity of life. However, a sudden onset of pain with no obvious reason severely challenges the ingrained response of pain equating to bleeding.

"You're constantly in a protective mode, aren't you, really. (Tony, 55)"

The constant balancing act of fear and concern over consequences contends with the immediate effect of bleeding being more pressing than seeing further into the future of weeks and months. This conflict of highly conditioned behaviour and internal dialogue about bleeding and its relationship with negative consequences then inhibits physical activity even more-

> *"The problem I've always had with exercise, gym, etc., is if you enjoy something you push yourself at it; and when you have problems with your joints and you're pushing all your muscles, you bleed into them and then you can't do it… it's just the annoyance that you're always back to square one..."(Greg, 39)*

There is a strong sense of the need to overcome the adversity and trying to make the best of the situation. This seems to be through a reflection of what has not worked in the past and forging ahead with what practically needs to be done in the present. This practical acceptance is noted by Healthcare professionals as well who view this perseverance as an adjustment that is ever changing and is embedded within the perceived identity of those with haemophilia.

4.4.2 Theme 2: Identity and self-agency – my normal is not normal

The sense of physical self and internalised perception of identity with, and because of, haemophilia has and continues to be influenced by internal and external factors.

4.4.2.1 Subtheme: Physicality and ableism

The bodily and perceptual changes acquired because of haemophilia start in early age. Whilst pain was a repeatedly intermittent feature, the reality of long-term joint damage and physical ability often developed slowly, to a point of sudden realisation of what was lost. The internal sense of physical self has for many with haemophilia been an ongoing salience for possible bleeding, but also with comparing their own view of themselves against unaffected peers. Reflection and reminiscence of being younger and what was '*their best years' (Andy, 40)* is common, often relating to feelings of having been more active and having less pain. But it is now viewed as a loss, because

such enjoyment with activity is fleeting and unlikely to be achieved with their current physical state. The reflective view of life activities is also mirrored in clinic consultations where smaller physical changes that have not been noticed by them are being highlighted.

> *"The physio said, "Can you stand on one foot and then do a toe raise?" I think, and it really kind of embodied that realisation of how debilitated my ankle joint was at that point that I could do that toe-raise on my right ankle, but I literally could not do it on the left because the ankle was so badly damaged." (Nick, 30)*

Men with haemophilia appear to want to be able to do more despite their physical limitations. They need support to do so, acknowledging the difficulties are physical, practical, and psychological because getting older with affected joints is hard and brings with it other issues of physicality-

> **"***There's no point in living longer if you're in a mess." (Hugh, 65)*

Even with support, issues with body image and environments that do not accommodate disability can impair physical activity even further and lead men with haemophilia to question the need to put themselves through this, trying to be active and manage pain with exercise becomes too difficult.

> *"I enjoyed swimming, but then I had trouble getting out of the pool. And then there's the embarrassment factor… trying to get out of the pool. So the arm is bent, I can't push myself up, and then trying to get out up the steps … I've got my feet planted just right so I can pull up on that." (John, 42)*

Choice of activity and ability/enjoyment is highly determined by physical attributes and assessment of risk. There are also deeper social and iatrogenic conditioning processes associated with danger and risk, intertwined with individual perceived ability, and belonging

> *"I think it just led to me thinking, "This isn't for me, this isn't where I belong," and never embedding that interest in me. You know, obviously, there's the sports, but there's also an exercise factor. I think they were kind of melded together in my mind as something that wasn't really acceptable or appropriate for me." (Nick, 30)*

4.4.2.2 Subtheme: Identity

Perceptions of identity in PWH are complex, existing in the social setting as well as implicit in their search for comparators to them and normalcy of themselves in day-to-

day life. Exposure to such views happens early on at school with their differences and social capital being negatively influenced by others in positions of authority.

> *I remember, the first day of secondary school, I was brought up in front of assembly, in front of 300 kids, and pointed at, and they said, "Don't touch this guy." The first day at this new school. "This boy, he's delicate and he bleeds." (Jack, 57)*

Whilst some learned to avoid 'trouble' by avoiding social contact that carried any risk of bleeding or injury, others were removed from school entirely to be home tutored, further highlighting their difference. Healthcare professionals appear cognisant about how early experiences haemophilia and treatment have shaped their patients view of their early life.

> *" A lot of those experiences were very… they would describe them as negative… They often don't want to talk about that until they have some other trigger… what they hate is what… the pain and things that they missed out that were very important to them when they were young. (Mary, Psychologist)*

There is a complex relationship with past experiences and how it influences their own social identity with their haemophilia, to the point where it has negatively influenced behaviours that they recognise could have been of benefit.

> *"I live in a really big student town. I joined the gym in July or August and all the students were away and it was marvellous. It was great… having that kind of window of opportunity to go and explore and begin to feel comfortable and use the machines and just having a play around, particularly having never felt like I belonged in those kinds of spaces, was really useful." (Nick, 30)*

As well as social identity perceptions there appears to exist a multi layered view of identity specific to haemophilia itself. Acceptance of the disease and its effects by both healthcare professionals and broader society is important, as being a person with haemophilia in itself is not how these men want to be defined, although there is acceptance that as a group "*the legacy is we have been damaged.*" (Hugh, 65)

Upward comparison to those perceived as normal appears to help strengthen their own perception of self with haemophilia, particularly in regard to pain, its intensity and their ability to cope with it. The pervading view is that PWH have "*experienced real pain*" *(Owen, 52)* and that those without haemophilia cannot begin to understand their experiences associated with bleeding.

There is a downward comparison made also, in that those without haemophilia who have poor surgical recovery for example, have not worked hard enough. This appears to relate to a perception that PWH know they have to work harder to recover, because they have had to do it so many times. Pain is as much part of the identity of a PWH as having haemophilia. Pain is normal, and life experiences embed the acceptance of pain within their view of themselves.

Whilst examples of upward and downward comparison appeared to be used to strengthen self-perceptions, comparing self with other PWH raised more uncertainty and questions about their own views and behaviours. Questions and self-reflection about participating in sporting activities revealed perceptions of never being "*one of those haemophiliacs that started playing football and then had to stop*" *(Leon, 28)*. There is also judgement about those with haemophilia who are at the other end of the activity spectrum, with an air of disbelief that high level sport such as cycling is even possible.

"We've got an extremist in our membership – Alex Dowsett" (Owen, 52)

In a modern era of better treatment, there appears to be a constant challenge to their view of themselves leading them to question if they should and are able to do more. Individual fears about pain and possible negative effects are confronted by seeing others like them with haemophilia having some positive outcomes with more exercise.

4.4.3 Theme 3: Haemophilia management and pain management is discordant

The assessment and management of pain, even as an acknowledged co-existing aspect of life with haemophilia is not viewed as being as effective as haemophilia medical care, even though trust in the team is high.

4.4.3.1 Subtheme: Experience, knowledge and understanding of pain

From an early age PWH and their families have been conditioned to use pain as a marker to evaluate/diagnose bleeding so as to initiate a management strategy. Active bleeding is painful but those with haemophilia have a well-rehearsed management plan, taught from a young age, which involves factor concentrate and rest/immobilisation. The 'if in doubt, treat' mantra was there to initiate clotting factor therapy as soon as possible to lessen bleed damage. The clinical language of warning

and danger is matched with behaviour of rest, subservience and waiting for resolution. However, in adulthood and in an era of less bleeding, this behaviour may be inappropriate.

> *"Unfortunately it is down to how we have historically managed haemophilia. The understandable advice always has been if you've got pain and you think it's a bleed, treat it… the parent gets lecture on this and then they instil that in the child …And then, by the time you're in your twenties or thirties, even, you're going to have quite a fixed view of what the cause of pain is." (Neil, haematologist)*

Healthcare professionals observe this behaviour and try to instigate a reasoned initiative to help, but this is with the knowledge that clinicians are likely to have perpetuated such behaviours from PWH by supposing that pain is probably bleeding.

> *"I think their go-to is, "This is a bleed," and I actually think there's quite a lot of undermanagement from MSK, because everything is put down to a bleed." (Rose, physiotherapist)*

The reality that pain may exist without bleeding requires some form of acceptance internally but is not necessarily accompanied by a suitable answer. Therefore, a newer developing form of interoception is required for those living or experiencing pain whilst on prophylaxis.

> *"I'm taking prophylaxis and all that, but it's still occurring. That can't really be a bleed; it has to be something that's happened down the line that's affecting my body now" (Adam, 28)*

Categorisation of their pain experience is used by PWH as a method of sorting through what needs to be done and how quickly-

> *"It's different. I think I sometimes class arthritic pain as just being an ache. Because of classing it in my mind as being an ache, I think I treat it differently to perhaps how I treat a bleed and what needs some sort of pain management."(Leon, 28)*

Treatment developments such as longer acting factor concentrates or interruptive therapies such as Emicizumab are changing the narrative of bleeding but also challenging what healthcare professionals believe they understand of pain in haemophilia.

> *"No one's able to prove exactly what happens, but do those little microbleeds make a difference? So, if your trough is able to be 5 or 10, does that make a difference? And I don't think we've got the science behind it." (Ruth, haematologist)*

The lack of a coherent 'why' when experiencing pain without bleeding, means many PWH believe they must accept it as constant.

> *"Patients tell me about experiencing pain and not being quite sure what it is and where it's coming from. I know that they have pain, but they sometimes can't quite put a cause to it, and so they talk to me often as if they're accepting that living with a degree… that having a degree of pain is what they have to live with, rather than it being something that can be changed."(Mary, psychologist)*

Whereas PWH have their own individual life story which feeds and moulds the narrative of their life lived with haemophilia, healthcare professionals rely on the experience of hearing and seeing those living that life to build a picture of trying to understand what that must be like. PWH tend towards a biomedical basis for pain being present, such as environmental provocations (walking on cobblestones), prolonged weightbearing activity, or bleeding. Healthcare professionals acknowledge these patient-reported 'reasons' but hear and incorporate them into their own reasoning model, helping better understand observed behaviour. Acceptance and awareness of the need for a whole person approach can, for example, give context to a more socially accepted view of pain for a reason (bleed), than none-

> *"I could see potentially how patients are self-diagnosing bleeds as a way of coming to terms or having a reason for their pain. And actually, if you're ringing up work saying, "I can't make it in today because I've had a bleed," that's quite different to, "I can't come in today because my pain is too bad." One is quite sort of acceptable and one is…" (Rose, physiotherapist)*

4.4.3.2 Subtheme: Care models and healthcare provision

A conflict appears to exist in the beliefs of clinicians and PWH in how pain is managed. Healthcare professionals appear to accept that patients are not talking to them about pain because they prefer to talk about other profession specific issues (e.g., medications with the doctor), whereas PWH believe that they are being asked tick box questions with no apparent interest in the issues that concern them (e.g. pain).

> *"The doctors, I'm getting "Are you taking your Celebrex? Are you taking your factor? Sorry you're in pain". And that's where the conversation kind of ends, and you get fobbed off to the physiotherapist." (Will, 52)*

Haematologists reflect that they play a role in the clinic setting that is dictated by what is asked of them by the patient, which revolves around medication prescription and factor usage. Clinicians in general accept the inadequacies of historical care provision

around pain in particular, and highlight the lack of any validated assessment tools or advice on good practice for pain management in haemophilia. In the absence of guidance, many are left to do whatever they want to do, and this is viewed as mostly unsuccessful and of low value

> *"I think… again, some of it will be that they don't have it in their armour to answer the question. And I think some of it is that they are going through the rhythm of clinic without really engaging in the whole process." (Emma, nurse)*

Assessment of pain is challenging. For some pain scales result in a contrived view of how they see themselves with their pain, given they experience their pain as a constant sensation. There is an overwhelming perception that such an approach is useful only for clinicians, and the value of such a score is changeable at best. PWH do not appear to value a VAS measure of pain as an informative assessment.

> *"I struggle with the 1 to 10 thing. Because, I mean, it's just pain. It's a different day. And I can't… I mean, I can imagine a 10, but I don't think I've had a 10. I can imagine a 10 because I'm a haemophiliac and I've had really, really bad bleeds. But I don't think that that was the worst bleed I could have had, necessarily, or the worst pain I could have had. So, I struggle with the 1 to 10 thing. I generally just toss it at around 6 and leave it alone. It's one of those questions that I don't know how to answer. (Will, 52)*

This perception of low value assessment of pain in clinics has meant that many PWH see their pain being something they can discuss more easily with their physiotherapist. The need to be heard and for a practical way forward in managing their pain is what is gained from interactions with physiotherapists. This need for a practical solution chimes with the way bleed management was practically solved by factor treatment. Now in an era when pain may not be a bleed and many men with haemophilia having no practical solution to hand that is not factor concentrate, they view the information from the physiotherapist as being useful in helping navigate their choice of intervention.

> *"The physio comes up with new, different ideas, you know, when you're running out of ideas: "You could use blah, blah, blah. Try this, look at that." So, it's a different angle on things." (Jack, 57)*

Physiotherapists themselves are accepting of this being a key part of their role and one that becomes increasing important to develop with in-depth experience of working with PWH. Pain is viewed by as constant feature of PWH but one that should be managed in a way as to enhance life and well-being.

"Because for a lot of patients their arthropathy is never going to obviously go away; there's only so much you can do. So, how do you help somebody to live with pain and function and have a quality of life as good as they can do? And not be dictated by their pain" (Kate, physiotherapist)

Clinicians recognise the inadequacies of historical care provision around pain in particular. Whilst confident in prescribing medication, they feel they have inadequate knowledge and skills to effectively manage chronic pain in its entirety.

"I think I feel confident in asking the questions. I think how you deal with it is a real… can be a real challenge because, yes, okay, there are certain painkillers that I know how to prescribe, but I'm not a pain expert." (Ruth, Haematologist)

Even with concerns about their own skills and knowledge, clinicians see the need for approaches to pain management to improve so as to enhance care and be considered a normal and effective part of clinical review and intervention choice. PWH need validation of their life experiences in relation to their pain as they want to be part of a solution that works for them.

"I think one of the things I've noticed, particularly over the last couple of years, is you're seeing doctors and physios kind of recognising that haemophilia doesn't just occur in a bubble. And it's been really nice to actually be given a bit more agency and responsibility to make decisions, and actively recognise that there is a lived context to what is possible. (Nick, 30)

4.4.3.3 Subtheme: Trust in healthcare professionals

Feeling safe, being listened to, and knowing that help in managing worries around living with haemophilia is available is important to PWH. Having the option of being able to call or drop into a centre is seen as a vital component of ongoing care for both receipt of medications, but also in working through symptoms of pain or bleeding that are not resolving as expected.

"for me, it's always been good to have the centre, where I can come and say, "Look, I'm not managing this. Something is wrong. I need help with it." (Tony, 55)

The trust placed in centres by PWH is primarily around knowledge and expertise in their condition, but also has a secondary issue relating to being seen immediately. Delay (or perception of delay) in an appointment is regarded as dangerous, reflecting the lifelong conditioned behaviour relating to bleeds. It may also be a reflection of PWH wanting to exert control in their lives with their disease as much as possible and having immediate help with pressing physical issues such as acute onset pain or possible bleeding is key to this.

"You can't afford to wait for the GP. You get an appointment in two weeks' time…" (Hugh, 65)

Attending any other healthcare professional who lacks haemophilia knowledge is regarded as ineffective. Such views are well founded in multiple previous experiences of PWH and their families, many of which have been negative and left trust shattered. This is a viewpoint shared by haemophilia healthcare professionals and one that also heightens concern for them if patients need to access other specialist services. Barriers to accepting advice or intervention from non-specialists are ingrained, with PWH conscious that this is due to the rare nature of their disease as well as the peculiarities of their physical complaints associated with it.

"I think I… I think haemophilia being reasonably quite a rare condition, I don't think… Having grown up, I don't have a natural trust of any and all clinicians to know why a joint might be the way it is, even if it's quite a generic… even if the joint is damaged in a very generic way." (Leon, 28)

Joint health and wellbeing in particular were noted to be issues that were fraught with risk or negative repercussion if managed by someone without knowledge or appreciation of haemophilia. The reality of not being heard and not being understood eroded trust in care, but could be bolstered someone who could inspire confidence in movement and physical ability.

"I always have much more confidence working with haemophilia specialist physiotherapists. I mean, again, as a kid you would get sent to the physio department for a bit of rehab post-bleed, and literally, they just didn't understand the context … it took me a while to trust the physiotherapists, that they weren't just going to force you to do something painful that you didn't really want to do." (Nick, 30)

4.4.3.4 Subtheme: Strategies for pain management

There is agreement with the healthcare professionals and insight from those PWH that strategies employed for pain management are shaped by the life experience of growing up with haemophilia. Pain has always been primarily associated with bleeding, and for the most part everything that follows is linked to both the successes and failures of how individuals chose to manage these events.

"Pain is danger. To me, pain means stop and treat yourself. And stop. (Hugh, 65)

Clinicians articulated that PWH coping and living better with pain in adulthood appeared to be linked to successes and acceptance of pain in their family and work life. Others reasoned that living with pain was more of a forced acceptance due to unsuccessful healthcare interventions.

> *"I think the patients that feel ground down by… it's often too many things at the same time, which are overwhelming for them. And then all the sorts of things that they've done to manage their pain are no longer working, because they're just too overloaded." (Mary, psychologist)*

In the acute episode of joint bleeding, there is little doubt that provision of clotting factor concentrate provides pain relief. The case for effectiveness of pain medications however is more complex and presents a dichotomy of thought between PWH and clinicians. Pain medications (often opioid based medications) in an era of no other treatment were standard. Older men with haemophilia have vivid distressing memories of becoming addicted, and such addictions being almost ruinous to their life thereafter. Younger men have also been socially conditioned to fear addiction from such medications, even when they could potentially be helpful.

> *"I was under the impression that having... taking painkillers if you had pain, especially in my ankle, meant I might then put pressure on the ankle before was ready to have pressure on it because it wasn't hurting as much. So, I never did." (Greg, 39)*

Side effects of such medications are remembered and recounted by many of the men in attendance including constipation, stomach ulcers, sleep interruption and wide-ranging effects on how they feel in their sense of self. Co-infection with Hepatitis C from contaminated blood products also raised concerns about long term liver health with pain medications and becomes another considered reason why such medications are to be avoided.

PWH want to be in control, even if that means being in pain. The avoidance of medication reflects a learned view that pain medications do not work for pain associated with haemophilia. There remains a gulf between what is needed in clinical practice and what PWH think and do in their day to day lives. There is insight however, that this knowledge of preferences and real-life behaviour comes only with better communication between both parties in relation to their pain.

> *"it feels like it probably is the lowest input from a clinical side, and we'll lose some patients, because if it doesn't work for them – maybe there are side-effects,*

maybe a particular drug or whatever doesn't work for them – they then won't come back and say; they will feel defeated somehow." (Mary, psychologist)

Options tried for pain relief exist on a continuum of good and bad consequence. Just to maintain daily activities and mobility PWH face a constant decision-making process as to how far to push and challenge themselves within the realms of their daily pain –*'So, it's almost like it's good, bad, but better. I think there is a lot to be said for keeping going sometimes, and just working through the pain to get to a better place.' (Tony, 55)* Although others view such decisions as inevitably ending in failure-

"… I actually am a bit eager and I have requested for physio/exercise referrals. I hope that the exercise would improve stuff, but what I've found is I jump on board each of these programmes with a bit of eagerness, I start trying to climb, and then I realise my joints aren't allowing it, and then I… and then I give up." (Andy, 40)

4.4.4 Theme 4: Uncertain about exercise but clear on what matters

When discussing exercise as a more specific component in managing pain, there was uncertainty as to rationale to do so. Even with pain there is an acceptance by some, that exercise may provide some positive influence on their wellbeing, however concerns over possible negative consequences based on previous experiences remain high. People with haemophilia identify function and less pain interference in day-to-day life as most important to them, and feeling supported to achieve this is essential.

4.4.4.1 Subtheme: Barriers, enablers, and the need for more proof

Avoidance of bleeding and by default perceived further pain is by far the greatest barrier to being more active and keeps PWH from taking the risk to do more.

"… at the end of the day, people just want to live a pain-free, bleed-free life, and probably taking… people think that taking the more static… not doing something is less risky than doing something. (Leon, 28)

These fears and concerns of PWH associated with activity is recognised by clinicians as a hurdle for both PWH in seeing a reason to do more with pain and for how healthcare professionals can facilitate a way through this mind set. However, it also presents the clinicians with a dilemma in that they feel as yet unable to provide 100% assurance that such an approach is indeed safe.

"I think the unknown is what level of exercise is safe – and I don't think we know that fully. I think we've got… all of us have got ideas, but I suspect there are clinicians who have got different ideas of what's okay to do compared to others. We've got patients who do their own thing too." (Kate, physiotherapist)

The fears of healthcare professionals about consequence and safety may well feed into the same fears of PWH, rendering interventions ineffective and poorly conducted. The language used by both PWH and healthcare professionals in relation to exercise is that of potential risk of bleeding and further damage-

> "*I'd need to know that I wasn't doing myself more harm, because I would expect it to be painful. And to me, pain is danger." (Hugh, 65)*

Societal barriers also influence views of exercise and activity and continue to do so even when PWH are wanting to do more. Much of these issues relate directly to a perception of danger and risk by others, and so add to both physical and mental concerns with exercise.

> *"Gyms – so, people who've registered with severe haemophilia and gone to the gym, and then the gym has gone, "Oh, no, no – you're not allowed to do that. You can't do that." (Emma, nurse)*

Maternal fears and accompanying behaviours on risk and danger in childhood have heavily influenced actions taken in adulthood. Others growing up with lack of treatment and constant fear of bleeding, now live with a fear of consequence that almost paralyses their ability to do basic exercise activity.

> *" a patient who lived in America, couldn't afford treatment so only treated for bleeds because his uncle sent the factor over… he has huge anxiety. He says himself he has forty pairs of shoes and it will take him half an hour to decide which pair of shoes to put on, because he thinks that will change pain and bleeds. He has a young child, a year and a half, and he's worrying how… I gave him some triceps exercises with a 200-gram weight, and he was too fearful to do those." (Rose, physiotherapist)*

Lack of motivation to change the current physical status quo is entwined with a sense of not understanding what could be achieved with exercise. Day to day activity that fulfils basic needs and requirements is seen as sufficient 'exercise' and the idea of further physical challenge and exertion makes no sense. There were however examples of facilitators to this activity also. Early positive childhood experiences of exercise created openness to its potential benefit as well as social and family observations on the importance of being active – even if their haemophilia meant they were not. Being reassured by the efficacy of prophylaxis on bleeding risk led to a rising sense of confidence in testing their physical selves in exercise activities, with a resulting increase in arthritic pain being judged positively as it was not bleeding. This

view is echoed by others who view an increase in pain as being less of an issue, as reassurance around bleed risk would encourage them to see exercise as an option-

> *"… if I need to have a bit of pain and it doesn't come with bleeding, to improve the condition of my joint, I would be more than happy to take that. I would take the pain knowing it's not going to cause a bleed. "(Andy, 40)*

For others, the journey to be more active and to use exercise came as a result of encouragement and perceptions of safety and permission from their physiotherapist.

> *"it's… you know, I've seen the changes taking place, and I've been encouraged by my physio that … they'll come up to me and go, "No, you can do all this, it's changed, you have good prophylaxis now." But it's taken a lot of mental work and energy to kind of overcome that and just feel comfortable. (Nick, 30)*

4.4.4.2 Subtheme: Practicalities, logistics and outcomes

Overall, both PWH and healthcare professionals were open and accepting of the concept of using an exercise approach in managing pain. For those that had previous positive experience with exercise and pain, there was a general acceptance that some more pain was acceptable in a longer-term view of overall benefit. There is a known and acknowledged anticipation of increasing pain, but it would improve – they have found a way to trust and permit themselves to do it, as well as trust the clinician working with them.

> *"I think it would be more pain, but I think the long-term benefit… In the past when I've done it it's… the benefits outweigh the pain. So yes, I think every so often it's good to push yourself a bit." (Tony, 55)*

However, others with no previous exposure like this wanted proof of effect before they would want to consider joining in with such activity, even though there was some acceptance of prophylaxis being there to prevent bleeding.

> *"If it was proven, yes, I'd give it a go. Because now I'm on prophylaxis, I feel that's some sort of a cushion." (John, 42)*

The need for reassurance was closely aligned to the requirement for information in order to make a reasoned and informed decision to participate. PWH are experts in their lifelong condition, and as previously highlighted, they are in a constant state of salience and decision making about all activities. Some need information to help

process a decision choice, whilst others view the information in a more practical acceptance of proposed benefits.

> *"if I was educated and shown proof that … you may feel more pain during the process, but it's not going to make you bleed and at the end you'll perhaps have less bleeds and less pain; if I was shown enough proof – and I don't know what that proof looks like – then I might be less concerned. But if you told me that I was going to feel more pain during the process, I would immediately be a lot more reluctant or sceptical." (Leon, 28)*

The need for information and reassurance stems from the requirement to be prepared for perceived risks and eventualities associated with haemophilia, from both PWH and clinicians. PWH expressed practical concern about which days and at what time the programme would take place, trying to envision how it would fit into daily life and in tandem with their prophylaxis regimes. Clinicians however were more concerned about what an exercise intervention would entail so that they could prepare treatment escalation plans (in case of bleeding or increased pain the day after exercise), as well as establish psychological support for readiness to participate.

PWH were clear that having someone they trust and who could understand their fears and anxieties was a key factor in how they would participate, as previous frustrations at non specialists had made them wary. Confidence in knowing they were being advised and shown the correct way to do exercises helped moderate deep-seated anxieties about further damage, risk of injury, and being safe whilst exercising.

> *"I think it's really important to have somebody to show you how to do it, and especially the fact that they were trained in this kind of thing was really… it really made me feel quite safe doing that. (Sean, 23)*

An improvement in function is rated higher than a decrease in pain - "*The function. I mean, the less pain, bonus, but it would be less pain in doing the things I want to do*." (*Will, 52*). An acceptance of pain does not necessarily mean there would be no will to have it eradicated if possible, but there appears to be a realistic acceptance of what matters most in their day to lives.

> *"I want to be kept going, I don't want to be cured, if that makes any sense. (Hugh, 65)*

4.5 Discussion

The aim of this study was to explore the views and beliefs of PWH and healthcare professionals on the lived experience of pain, and how this may influence perceptions of using activity and exercise as an option in its management. The account presented here highlights that for PWH pain is a lifelong, continually evolving experience and deeply influenced by social, cultural, and medical experiences within that lifetime. Many PWH have moderated and accommodated their pain into their daily life, thus positioning them with a unique set of expert experiences in their own management. A greater understanding of these experiences may help inform interventions that are meaningful to all involved in the therapeutic encounter.

To contextualise an understanding of the pain experience in PWH, it is important to understand the historicity of such experiences within a timeline of medical treatment. In the 1950's/60's management of acute musculoskeletal bleeding was limited to bed rest and access to transfusions of whole blood or fresh frozen plasma (16). With the development of effective treatment in the form of Cryotherapy in the 1970's, pain associated with acute bleeding was seen as something to be managed in co-ordination with bleed management and resolution, whilst chronic pain presented 'considerable therapeutic difficulty' (151) with advanced haemophilic arthropathy management viewed as a palliative endeavour (152).

Children with haemophilia in an era of limited effective treatment were noted to have a deep understanding of existential issues relating to pain and the effect on their family. Spitzer and colleagues (1992) observed that boys with haemophilia aged 8-10 appraised fears about their condition and its bleeding symptoms within a construct of reality based on their previous experiences (276). Whilst they expressed sadness with the pain, immobility and threat of death associated with bleeding, they were able to counter these emotions in expressing happiness at end of treatment (Cryoprecipitate) with a decrease in their pain and suffering from the bleed. They developed coping strategies that were relevant and productive and associated with minimising the event (bleeding).

The consequences of childhood pain on parental emotions are also challenging, and those in this study were all very aware from a young age how their condition affected

their family. Managing unpredictable challenges such as bleeding and pain for mothers of boys with haemophilia was beset with distress (277). Similarly, parents of children with Juvenile Idiopathic Arthritis report desperation in trying to manage painful episodes associated with the illness, and the physical and emotionally draining effect on the entire family and family life being affected (278). The fear of a child being in pain and the ever present feeling of potential danger traps parents in a 'cage of fear', resulting in an ingrained behaviour of always thinking about possible consequences (279). The constant surveillance for pain and danger is not only confined to parents. Young people with sickle cell disease report that they are always monitoring for signs of sickle crisis and pain so as to be ready to take action with it, but are mindful as to when and who to disclose it to so as not to be marked out as different or disrupt their life (280). It is notable that there are similarities in such behaviour seen now in adults with haemophilia. Whilst they contemplate their pain and the ever-present fear of bleeding, how they choose (or not) to communicate about their pain also impacts on their own family as they try and manage their perceived burden of themselves on others.

Physical activity, due to its associated risks with bleeding, was curtailed in the formative years of many PWH. Others have reported similar finding to those here in regard to PWH being prevented from participating in school sports and activities (138, 281). Whilst this imposed difference was unwelcome and stigmatising, many PWH still feel guilt that their own actions at the time have added to their experiences now of pain and functional difficulties (282). In their qualitative study in men with haemophilia, Rolstad and colleagues found that older men with haemophilia carry a psychological burden that is influenced by the degree of social stigma and ignorance they encountered in their formative years (283). Whilst the cohort in this study are able to recount negative experiences of their life and pain associated with their haemophilia, it appears to be situated within a coherent, reasoned and somewhat positive account of that life – and one which makes sense to them and others with shared experiences. This is perhaps an extension of the coping strategies developed in childhood, but it may reflect acceptance of what is felt to be currently realistic. A large ethnographic study of PWH in five countries, highlighted that although there is a trade off with pain and the need to stay active, there is a view for many that things used to

be worse, and that this perhaps prevents many from being able to live their fullest life possible (284). This lived experience of what was, alongside their individually appraised experiences of everyday life continue to influence how pain, function and activity exist within a desire to avoid bleed provocation at all costs.

Whilst living with a rare congenital condition can bring with it a burden of disease management and its sequalae, many do not wish to be defined by that condition. The participants in this study spoke with clarity on how their haemophilia does not define them and that living with haemophilia is their 'normal', for it is all they have ever known. Similar to others reporting the same phenomenon (227, 285), participants here expressed a belief that PWH are conferred with an enhanced pain tolerance due to their many previous experiences of pain, and this for many was how they reasoned with their ability to live with pain the way they did. Whilst Kalmar and colleagues developed this association further, by highlighting that older men with haemophilia actually learned to be dismissive of pain that was not related to their haemophilia (286).

It is the association and identity of having pain alongside their haemophilia that is a notable exception in this study. The findings here suggest that for many PWH their identity as a person with chronic pain is as much a part of their identity as haemophilia is. Some recent studies have highlighted that even in era of access to better haemophilia treatment, some cohorts of PWH report a lifetime of pain and an associated significant interruption to life because of this pain (69). Such reports are mirrored in the multi-national Hemophilia Experiences Results and Opportunities (HERO) study where quality of life and inability to do activities of choice were negatively affected by pain (116). Whilst some broad similarities were found in our data, many of the men interviewed here appeared to be accepting of what they were able to do with their pain being present and had altered their lifestyle accordingly. It is unclear if this is particular to this group of men included in this study, or perhaps a wider indication of access to both haemophilia treatment and experienced healthcare teams.

Although PWH feel that issues relating to their pain are not captured in current haemophilia clinical setting, they also do not feel comfortable going elsewhere to other non-haemophilia specialists for pain advice, and so therein lies a conundrum.

Haematologists and haemophilia centres are considered the primary port of call for pain management advice by PWH (66, 128). However recent studies suggesting clinicians tend to underestimate pain in PWH (61, 66) may help contextualise the reports of those PWH who feel their pain is poorly managed (69). The findings here suggest that such views could be explained in part, by the fact that although healthcare professionals acknowledge the need to be able to manage pain within the haemophilia MDT, there is a perception that they do not have sufficient skills and knowledge to help PWH in their clinical care. This phenomenon has not been well documented to date, however one qualitative study investigating haematologists experiences of managing PWH highlighted the difficulties faced with balancing being an expert in the disease area with the struggle of having to take on other multiple roles but without the necessary knowledge and skills (287). It is clear that both clinicians and PWH need to find a way to work better together in managing chronic pain, to see people as more than their presenting condition and to identify care concerns and input that is meaningful to all (265).

The lack of a coherent pain assessment in PWH that encompasses both physiological and psychological aspects has been highlighted (79). For the most part, routine pain assessment has been biomedically focussed on measuring intensity (VAS, pain rating scales). For acutely painful musculoskeletal bleeds this is a reasonable approach, and one that PWH find acceptable (288). However, for ongoing chronic pain, measuring intensity alone has limitations in PWH (289) and use of such approaches misses the deeper lived experience and meaning of pain for an individual (290). The findings here highlight the perceived low value that an intensity-only pain rating has to PWH and chronic pain. Functional impairment and life disruption because of pain were felt to be more relevant and so should be the focus of chronic pain assessment in such individuals.

To date there remains no actual evidence of efficacy of any particular medication for chronic pain in PWH. There has been an issue historically with the use of opioids for pain relief in PWH although there is some data to suggest this is less of an issue currently (265). Although the recently updated haemophilia treatment guidelines from the World Federation of Haemophilia highlight pharmacological management as a first line in acute and chronic pain (111), the participants in this study reported a dislike of

pain medications and avoided taking them it at all possible. Perceived non-effectiveness and the dislike of how they made them feel were different to the reasons given in another qualitative investigating masculinity in haemophilia, were avoidance of pain medications was because taking them was viewed as an outward sign of their disorder (285). Witkop and colleagues in their questionnaire study of PWH in the USA, noted only 28% took their pain medications as prescribed (126). Whilst worries about toxicity and lack of effectiveness are common (291) a finding across multiple studies was that if people felt listened to, given appropriate information and were part of the decision making, then adherence and use of pain medications was better (291-293). Healthcare professionals need to understand the life experiences of PWH to contextualise why they may not want to use pain medications and counsel them appropriately if they are felt to be of use in discrete situations.

Clinicians acknowledge that a historical focus on bleeding as the predominant source of pain has made it difficult for PWH to reason other non-bleed reasons for pain (such as arthropathy). Other studies have noted that PWH report using factor concentrate for both acute and chronic pain which supports this clinical view (69, 126). However, those same studies also describe a wide range of management strategies employed by PWH that focus on complementary and alternative medicine approaches and passive activities such as rest or relaxation. Further, the use of physiotherapy as a management option is reported as no more than approximately 30% across a multitude of studies (66, 105, 115, 128). The findings here appear at odds with this previously published data with participants highlighting that access to physiotherapy was a way of fulfilling the desire for a practical, problem-solving approach to their pain. Also, as all participants were on regular prophylaxis, an increase in factor usage for pain was not seen as a valid strategy most of the time.

Planning, strategizing and careful organisation of day-to-day activities is a key feature of everyday pain management for PWH. The need to try plan for all eventualities when living with pain is a common finding in other qualitative haemophilia studies (286) as well as those in RA (294). This level of planning is also viewed as normal for participants in this study, and highlights the importance of understanding an individual's current management strategy before embarking on offering advice for another. An in-depth qualitive study looking at views of self-management in a cohort

with OA found that a major drive for self-management was the need to establish order in the disorder imposed by their disease. More notable however, was their conclusion that the meaning of self-management for participants in their study did not involve education by health professionals nor necessarily the adherence to medically prescribed treatment regimens (295). This finding may help illuminate why such a wide array of management strategies are described by PWH in previous studies, highlighting further the importance of clinician and PWH working together for better management of pain.

'No Aspirin, No Injections, No Exercise' was a common sign seen above the hospital beds of PWH in the 1950 and 60's, when treatment for active bleeding episodes was limited (14). Exercise was synonymous with risk and danger of bleeding, and as a result many people went into adulthood with a view that being too active was risky. The narrative histories of those in this study reflect these past experiences, which are also now being interwoven with trying to navigate and make sense of their chronic pain. The association between risk of musculoskeletal bleeding and physical activity perpetuates even in an era of improved haemostatic treatment. This historical reference point and the personal beliefs developed thereof for many PWH, sits rather awkwardly against a current biomedical paradigm that promotes physical activity for health benefit.

Whereas other arthritides such as OA and RA have demonstrated self-management approaches using cardiovascular and strengthening exercise, education and coping skills to be useful adjuncts in pain management (187-189, 296), it remains unclear if this is a safe and feasible approach for PWH. Unlike people with RA who expressed a fear of exercise making pain worse and causing more damage (297), the primary concern voiced here was the uncertainty and meaning of pain sensations. The fear is that being active with pain may provoke bleeding, as well as anxiety that the pain being experienced may actually be a small bleed that could be made worse with being active. This relationship between pain and bleeding has been explored by others who also noted activity avoidance, perhaps somewhat understandable in this context, was a key strategy in managing those fears (269, 282, 284). Acknowledging and understanding the fears a PWH may have around their own pain sensations with

exercise is important so as to formulate effective and mutually trustworthy interventions for pain management.

Understanding and acknowledging unhelpful iatrogenic messaging around activity and exercise is also important, as it may play a key role in preventing PWH from participating. A qualitative study investigating what healthcare professionals perceived PWH needed to know in order to better manage their condition failed to acknowledge how the previous experiences of PWH may influence behaviour around physical activity. The study also highlighted how healthcare professionals can give mixed messages about physical activity and exercise – on one hand advising that PWH need to be more healthy with physical activity, then caveated with a message about the risks and dangers of bleeding with activity if prophylaxis was not maintained at an appropriate level (298). Hughes et al in their ethnographic study of men with haemophilia did identify a difference in priorities from treatment between PWH and healthcare professionals (284). Whilst healthcare professionals had a focus on adherence to prophylaxis so as to achieve zero bleeds, PWH saw prophylaxis as being contingent on how it achieved their own meaningful goals and activity. Awareness of such language and perceptions are not just reserved for those with who are older with multi-joint haemophiliac arthropathy. In a small qualitative study with young men aged 18-25 with haemophilia, it was highlighted that physiotherapy was too biomedical in its approach and did not focus enough on fitness and wellbeing, especially in relation to muscle training (299). If physical activity and exercise has the potential for benefit in PWH with pain, it is imperative that messaging about participation is framed in the context of modern haemophilia treatment and not be reflective of now historically inaccurate representations of haemostasis.

Chronic pain in PWH is becoming more widely recognised as a moderator of physical activity, and by extension for some, planned exercise. Participants in this study were open to the possibility of trying exercise as a treatment option whilst having pain. However, they highlight that their reason to do so related more to being able to function better rather than cessation of their pain, which they acknowledge is unlikely to be 'cured'. In a qualitative study of men with haemophilia, Taylor et al (190) reported that their cohort had a very positive approach to exercise and physical activity and adopted positive coping strategies towards it. This is in contrast to the

cohort in this study who appeared more wary of being more active with exercise even though they could reason the benefits. This may be due in part to the participants in this study being recruited due to identifying as having chronic pain, whilst those in the Taylor study were noted to be positive towards physical activity and exercise as a group. One notable similar finding however, was the need to focus on what activities can be done, rather than what to avoid, with a similar focus on enjoyable non-traditional exercise activities (gardening, DIY, walking) being noted in another study by the same author (269).

4.6 Reflexivity

Reflexivity is integral to the qualitative research process, and can be considered thoughtful, conscious self-awareness (300). An awareness of the position of the researcher in qualitative approaches is important as it can impact the research process in three ways; 1. Access to the field – this can be where participants are more willing to share their experiences with someone they perceive as sympathetic to their situation; 2. Shaping the nature of the researcher/researched relationship – this affects the information participants are willing to share; 3. The worldview and background of the researcher – this can affect the way in which the researcher constructs their world view, uses language, poses questions and chooses the lens from which to filter information through (301). In being actively reflexive, the researcher recognises the potential effects of their own philosophy, beliefs, feelings and personal experiences may have on the research process and outcomes (302).

I am a white, male physiotherapist who has worked at a large, world renowned haemophilia centre in central London since 2006. The qualitative inquiry described in this chapter was part of my doctoral programme and was designed with support from my research management team. Whilst there was patient involvement in the development of this programme of PhD study, I was aware of my own perception of owning the research approach as well as a desire for novel findings to be an outcome. I was initially uncertain as to how my extensive clinical experience and knowledge of haemophilia would sit alongside my relative inexperience in conducting focus groups and interviews, and if there would be a risk of me potentially leading participants, or misrepresenting their stories. Acknowledging and being more aware of these potential

facets of the process helped me discuss them openly with the research team throughout the process.

I was known professionally to all of the healthcare professionals interviewed and to nine of the participants with haemophilia. As haemophilia is a rare disease with care provided in a discrete number of centres in the UK, it is unsurprising that professional relationships with clinicians would be present. The haemophilia participants already known were either currently or previously registered at my clinical place of work. Whilst it is conceivable that such existing professional and clinical relationships may introduce bias in the process, it was clear from the discussions and responses given that both positive and negative experiences and views of care received were easily shared. The focus groups also had a second moderator present (clinical supervisor, KK) who was not known to the participants, but did have an extensive knowledge of haemophilia. I made written notes and reflections after the focus groups and interviews, as well as in the months during analysis of the data. There were also many discussions with KK (clinical supervisor) following the focus groups about the process, my thoughts and feelings as to my approach and level of engagement within the group. There was rumination too about some of the more negative comments from participants about the service I had worked in. This provided some challenge for me to reflect on my views of that care provision, and to consider what part I had potentially played in the experiences being recounted. In highlighting some of my own latent assumptions, I feel my engagement with the data improved to the advantage of the findings reported.

A researcher led, reflexive thematic analysis approach to coding was employed here, rather than that of coding reliability or use of a codebook. This may mean other researchers who would come to analyse this dataset with a different philosophical position or clinical experience to that described for me, may come to different conclusions. This in itself is not a limitation, but elucidating my position as a clinician and researcher in this study acknowledges that which influenced and informed the research process.

4.7 Trustworthiness

The findings of qualitative research need to fulfil established criteria to be considered trustworthy. Researchers must demonstrate that the data analysis has been conducted and recorded in a precise, consistent, and exhaustive manner so that a reader may determine whether the process is credible (303). To parallel the conventional quantitative assessment criteria of validity and reliability, Lincoln and Guba proposed that trust in qualitative research is judged on five criteria: Credibility (recognition by the reader of the process used/experience described when confronted by it), transferability (the degree to which findings can be transferred to other settings), dependability (research process is logical, traceable and clearly documented), confirmability (the findings and interpretations presented are clearly derived from the data) and reflexivity (a clear process of critical self-reflection) (304, 305).

Familiarisation and immersion in the qualitative dataset is a key starting point in reflexive thematic analysis. In applying this time and process with deep and thoughtful analysis of the extensive transcripts produced in this study, the credibility of the findings reported here do fairly represent the data, as evidenced by the use of multiple quotations throughout the narrative. Information about the participants (age, geographical location, diagnosis), setting of the focus groups/interviews, the methods used (including the topic guides) and the quotations and the story they help to tell, provide thick description upon which the reader can evaluate transferability to other contexts. The evaluative processes I used from data acquisition in deriving the codes and subsequent theme development is well described in the methods section, with a clear process of how I came to the conclusions presented. The reflexive process described above also provides an overview and explanation of my own position and values as I carried out this research study, and therefore provides a justifiable basis for the trust that can be placed in the results presented here.

4.8 Strengths

A strength of this study was the condition specific and academic experience of the team. In a rare condition such as haemophilia, the need for this balance is important so

as to drive forward quality research approaches that are also relevant to the people taking part in them.

The inclusion and active participation of a person with lived experience (CS) in the development of the topic guides for the focus groups and interviews helped finesse the aims of the sessions as well as the direction and reasoning for the questions. As part of the overall research management team, CS also played an equal role in the conversations about the researcher's reflexivity as well as discussions about the development of the thematic structure.

Whilst the participants with haemophilia were homogenous in their diagnosis of severe haemophilia, they did represent a wide range of experiences of healthcare that included NHS and non-NHS settings. This added dimension of experiences in countries with limited access to adequate prophylaxis brought depth to the focus group discussions, and also helped to deepen the researcher's understanding of the overall lived experience.

4.9 Limitations

Despite the strengths of this study there are acknowledged limitations. All of the participants included in this study were resident in the UK and therefore receiving what would be considered world leading haemophilia care. It is acknowledged that those PWH in low resourced countries, and in healthcare systems with limited or no access to effective haemophilia treatment may not have the same experiences or beliefs expressed by those included here. A strength, however, is that some participants did not grow up in the UK and so were able to express and discuss their experience of pain from that perspective. Further research should be mindful of the socio-economic and cultural influences of healthcare on the individual experience of pain in PWH.

This study only included people with severe haemophilia. This is in no way to diminish the experiences of those with moderate or mild haemophilia, but it remains that those with severe haemophilia remain most likely to experience more episodes of bleeding and painful joint damage from a young age. It is imperative therefore to understand these experiences. Further research should seek to explore if people with moderate

and mild haemophilia have similar or differing life experiences of pain as well as thoughts and beliefs relating to pain.

Another limitation may be the number and variety of healthcare professionals who took part in the interviews. Whilst it is possible that increased numbers of profession specific participants would have provided further data, time and resource available for to this study were limited. However, all professionals participating were expert clinicians in haemophilia care, working at five different haemophilia centres. Given that haemophilia care is delivered by a multi-disciplinary team, it is considered that the views expressed represented a broad view of work practices and experiences.

4.10 Conclusion

Pain is a well-established feature of acute bleeding in haemophilia. This study highlights that early experiences of bleeding and persistent pain associated with joint arthropathy may play a role in how pain becomes embedded in the life experience of living with haemophilia. Continuing to view pain as a wholly biomedical construct fails to appreciate and understand the effect of multiple unique pain experiences that PWH live with.

The need for improved, effective, and meaningful pain management strategies are much needed for PWH who live with longstanding chronic pain. Pain assessment remains perceived as low value, and is coupled with the fact that healthcare professionals in haemophilia feel ill-equipped to engage fully in the process. Even with this dissonance, there is substantial trust and well-established therapeutic relationships between those with haemophilia and their healthcare team, providing an excellent foundation on which to build better pain management approaches. PWH want to feel reassured in doing activities that matter to them. Healthcare professionals in haemophilia should be mindful of the individual's lifetime experience of pain in clinical encounters and seek to understand its relevance to practice and any interventions that may be required. It is imperative that pain management approaches are situated within an understanding of the individual's lifetime of pain experiences, framed in the context of modern haemophilia treatments rather than historically

inaccurate representations of haemostasis and designed around personally identified goals and functional aspirations.

This chapter has presented a rich and contextual understanding of the lived experience of pain in PWH and healthcare professionals, and highlights the positive view of exercise as a potential approach. Chapter 5 describes the development process for a stakeholder informed theory that will underpin the REMAP-Haemophilia intervention.

Chapter 5 - Theory development and intervention modelling

This chapter will revisit the concept of a complex intervention and how the REMAP-Haemophilia study conforms to the definition of being a complex intervention. The definition of, and requirement for, a process model and programme theory will be introduced, and the 'Theory of Change (ToC)' approach used to create a theory will be defined including the involvement of stakeholders in this process. The method by which a theoretical model of behaviour change (the COM-B) was mapped into the stakeholder created theory will be described. The outcomes of the theory map and the behaviour change techniques to be included in the study protocol for testing in the feasibility study will be presented and discussed. A brief description of the REMAP-Haemophilia study will then be presented at the end of the chapter, setting the scene for the following chapter describing the methods in-depth.

5.1 Developing a complex intervention

A detailed overview of the Medical Research Council (MRC) framework for complex intervention development has already been provided in Chapter 2. Of relevance to this chapter is the recognition and inclusion of context, theory development and stakeholder involvement as core elements of the framework (196). Awareness of the contexts and constraints in which an intervention may be operating is an important consideration in complex intervention development (306). Meaningful engagement of stakeholders in theory development maximises the probability of developing an intervention that delivers meaningful and positive impacts on health (196). This co-production approach can help identify critical aspects of an intervention and how they may be related, further strengthening real-world applicability (307). The method used here engaged stakeholders in the process of developing a theory that would underpin the protocol for the feasibility study.

5.2 Theory development

Personal intuition is often biased and limited in scope, and so formalising the theory of an intervention enables maximum exploitation of learning, accumulation of knowledge and promotes transfer of learning from one project to another (308). The basic logic of theory driven evaluation is simple, in that evaluation seeks to discover whether an intervention works, therefore the programme is in itself, theory (309). The

development and explication of theory is valuable as it explains the intervention outcomes, predicts how implementation may unfold and can support the generalisability of research findings across a range of settings (310). This space between the intervention and the expected outcome, known as the 'black box', is full of multiple potential theories that need to be made explicit. Doing so enables better understanding of the 'how' and 'why' an intervention may have the effect observed. (192).

5.3 Programme theory

Programme theory is the construction of a plausible and sensible model of how an intervention is supposed to function, is practical and specific to each intervention, and justifies the intervention in terms of its expected casual effects (308, 311). By starting with a programme theory, it is made clear just how many and varied the processes are that may lead to an intervention's success or failure (309). Without it, it is impossible to know if the aspects of implementation quality and quantity have been measured correctly (312). A well-defined programme theory helps bridge the space between empirical observations and the mid-range theory used as a framework to understand the problem at hand (308). (Figure 21)

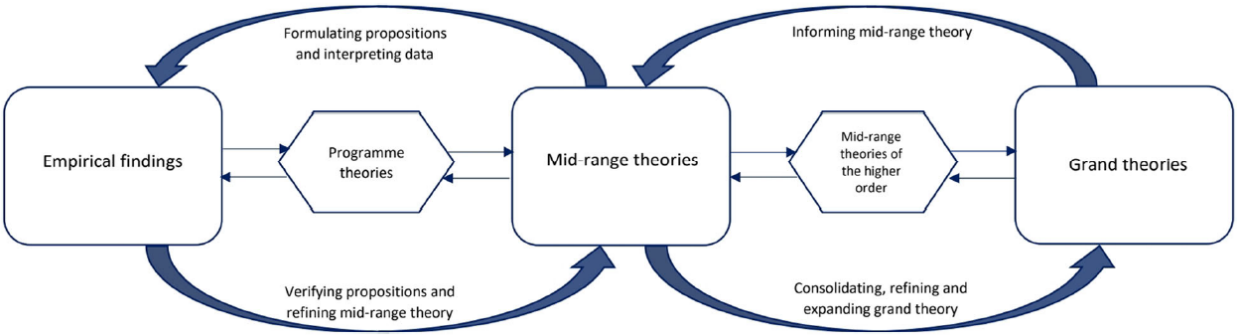


Figure 21: The bridging role of theory in the process of scientific enquiry (From Kislov et al 2019)(310)

Programme theory can be expressed as process models, logic models or frameworks, and are a fundamental tool of theory informed, logic driven intervention design and evaluation. Their purpose is to summarise key programme elements that include the programme assumptions, programme activities as well as the inputs, outputs and

outcomes (313). A good programme theory should include both a theory of change and a theory of action (314), although there are different methodological approaches in how to approach these aspects and in how they are presented visually as process models.

5.4 Logic Models

A logic model is the visual representation of the programme theory. At its basic level it provides an 'at a glance' description of the intervention that includes the inputs, activities, outputs, intermediate and long term outcomes along with the programme assumptions and context (315). Whilst they often include directional arrows to represent apparent cause and effect, there is often little or no explanation for how or why these causal assumptions exert their effect. Thus, one of the main criticisms of logic models is that due their linear and mechanistic presentation, they oversimplify the context in which a programme operates and the predictability of an outcome (307). This artificial representation of reality can be combatted by accepting that complexity is present, and there will be multiple perspectives of the experience of the intervention, allow more meaningful and useful evaluations (313).

5.5 Defining the Theory of Change approach

Theory of Change (ToC) is a theory of how and why an initiative works. It should involve stakeholders, and combines logical thinking (sequencing an initiative from inputs to outcomes) alongside deep critical reflection of values, worldviews, assumptions and philosophies as to why and how a change may happen because of the intervention (193).

More often associated with large international development projects, in recent years healthcare researchers have begun to use this process approach in the development and evaluation of interventions (314, 316). Laing and Todd describe four models of ToC development; a deductive model (where theories are developed from existing research); an inductive model (where theory is built from observing phenomenon); a mental model (which privileges the knowledge and experience of stakeholders); and a fourth collaborative model where the researcher takes the position of a critical friend (with a support and challenge role with stakeholders) to co-create the ToC based on existing research evidence and the personal expertise of stakeholders (317).

Whichever model is used the minimum elements of a ToC should be (193) :

1. Context and acknowledgement of existing change processes and the 'actors' able to influence change
2. The long-term change that the intervention seeks to support and for whose benefit
3. The processes and sequence of change anticipated to lead to the desired outcomes
4. Assumptions about how these changes might happen
5. A diagram and narrative summary that captures the outcomes of the discussion

The narrative summary is necessary to provide further explanatory detail about the ToC as well as highlighting any elements that are not included in the model itself. It should include (318);

- the *context* of where the intervention will occur (the people and the places);
- the *assumptions* that detail why it is thought one outcome will lead to another;
- the *evidence* that supports the activities, as well as that which shows that one outcome leads to another;
- the *enabling factors* that need to be in place for the ToC to happen as described, in particular relationships and engagement of the target audience and the perceived quality of the activity within the intervention.

5.6 Stakeholder participation in developing a Theory of Change

Choosing an approach that actively involves and values the input of stakeholders such as patients and clinicians when building a ToC model requires that the stakeholders get together to interactively discuss and create the map. The ToC approach works well when considering a complex intervention and privileges the views, beliefs and experiences of the actors involved in the intervention (the designers, those that receive it and those that will deliver it). As a pragmatic framework, ToC complements the intervention development phase of the MRC framework, and importantly, can accommodate other theories to explain causal links and improve development of research projects (316). (Table 9)

Table 9: The Theory of change (ToC) model and the MRC framework (Adapted from DeSilva et al. 2014) (316)

MRC Framework Domain	Theory of Change Strengthening
Develop Intervention	1. Improves intervention design through: • Consensus building with stakeholders • Designing interventions with aim to cause real world change • Embed intervention in context • Provide a frame for 'theory' 2. Create realistic expectations of impact of intervention – as stakeholders have to compromise on what outcomes are possible within context and resource
Feasibility	1. Identifies research questions by highlighting knowledge gap 2. Highlights barriers to implementation early on and helps develop strategies to overcome them 3. Improves piloting by providing evidence of links between early project activities and short-term outcomes to refine the intervention design
Evaluation	1. Allows for multiple pre-specified outcomes 2. Combines process and effectiveness evaluations 3. Helps disentangle which intervention components are most effective by explicitly measuring the impact of each intervention pathway
Implementation	1. Improves dissemination of results with a powerful visual, common-sense tool which can be used with range of stakeholders • Providing an intervention description • Enabling local buy-in and adoption of results • Illustrating the 'active ingredients' of intervention to facilitate adaptation in new contexts

Other mid-range social or psychological theories such as behaviour change theory can be integrated into a ToC framework. This strengthens the explanations for observed causal relationships, increasing the ability to explain 'why' and 'how' an intervention has its effects. The inclusivity of process and the transparency by which a ToC is conducted, as well as the ability to integrate behaviour change theory made it an appropriate methodological approach for use in the development of the REMAP-Haemophilia feasibility study.

5.7 Behaviour change theory

In developing complex interventions that aim to elicit behaviour change, there is a need to use a method that incorporates an understanding of the behaviour to be changed and uses a system that characterises the interventions and their components (319). Theories of behaviour change can help identify barriers and facilitators to change as well as mechanisms of action. The COM-B model and the Behaviour Change Wheel (BCW) is considered a middle range implementation theory, in that it helps explain what may influence outcomes, allowing developers of interventions to understand the process at hand and inform future iterations (320).

The BCW is a synthesis of 19 frameworks of behaviour change (Figure 22). At its centre is the COM-B model, a theory of behaviour change that posits behaviour (B) is moderated and influenced by the interactions of capability (C), motivation (M) and opportunity (O) (321) (Figure 22):

Capability is considered an individual's physical and psychological capacity to engage in the activity concerned, and includes the person possessing the necessary knowledge and skills;

Motivation is viewed as the brain processes that energize and direct behaviour. These are not only goals and conscious decision making, but include habitual processes, emotional responding, and analytical decision making;

Opportunity is all the factors lying outside of the individual that make the behaviour possible or prompt it (319).

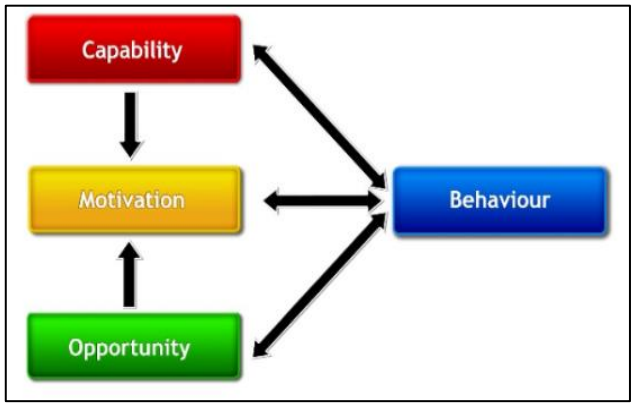


Figure 22: The COM-B model of behaviour change (From Michie et al 2011) (319)

The next layer in the BCW represents the 9 behavioural intervention functions (education, persuasion, incentivisation, coercion, training, enablement, modelling, environmental restructuring, and restrictions) that target one or more of the COM-B components to change behaviour. These intervention functions are linked to specific behaviour change techniques. The outermost layer describes policy categories that can help deliver the functions at a wider population or policy level.

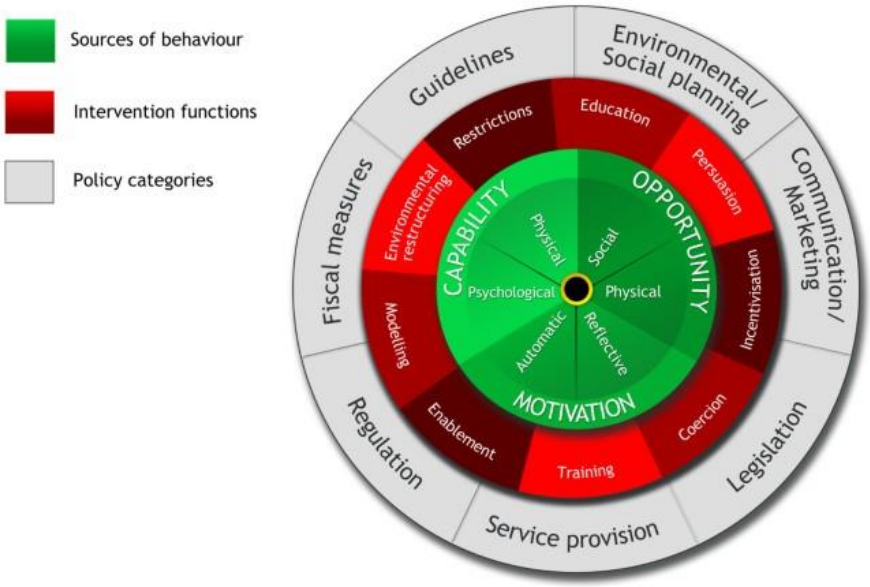


Figure 23: The Behaviour Change Wheel (319)

A behaviour change technique (BCT) is an observable, replicable and irreducible component of an intervention designed to alter or redirect causal processes that regulate behaviour i.e. a technique proposed to be an active ingredient within the intervention (322). A taxonomy of 93 BCTs was created in response to the lack of agreed labels and terminology being used to describe intervention components, and in doing so has created a structured system that is relevant to a wide range of behaviour rather than being restricted to just a single behavioural domain (322). Behaviour change techniques operate as intervention functions with the BCW, and can be used alone or in combination with other BCT's (321).

5.8 Operationalisation of the BCW

Prior to implementing the BCW a behavioural analysis is completed. The premise is to understand the problem at hand in behavioural terms, and is informed by the best current evidence available including literature reviews and qualitative insights. This stipulates the behaviour to be targeted, where it occurs and who is involved. Using COM-B, a "behavioural diagnosis" is then formulated which aims to form a judgement on what needs to change. The "behavioural specifications" for the target behaviour is then devised which allows the identification of the intervention functions on the BCW and subsequent BCT's which can than target the behavioural change. When the list of BCT's is complete, it is then reviewed and narrowed down using the APEASE criteria; Affordability, Practicability, Effectiveness/Acceptability, Side-effects/safety and Equity (321). This process further curates those BCTs to be included in the design of the intervention and draws focus to the real-world applicability of implementing the intervention. This process will be used to develop the protocol to be tested in the feasibility study.

5.9 Aims and objectives

To develop complex interventions which are more likely to be effective, sustainable, and scalable, it is important to understand not just whether, but how and why, the intervention has a particular effect, and which parts of a complex intervention have the greatest impact on outcomes. The aim of this study is to:

- Describe how a dialogue-based stakeholder process will generate a theory of change
- Define a theory using a collaborative model (theory of change map) that will inform the design of the REMAP-Haemophilia intervention.
- Identify behaviour change techniques to be included in the intervention design
- Refine the proposed REMAP-Haemophilia intervention ready for feasibility testing

5.10 Methods

5.10.1 Recruitment/ Volunteer to stakeholder group

Recruitment to the stakeholder group comprised people who had participated in the earlier qualitative study who had expressed an interest in participating in further work

associated with the study's aims and objectives. One physiotherapist contacted the researcher expressing an interest in taking part in this project after hearing a presentation about the overall aims of the research being planned. Those PWH and physiotherapists were approached via a brief email to ask if they were still interested, and if they would like to be part of this theory development process. Those who agreed were sent a follow up email with a detailed description of the workshop aims and objectives, the time commitment required from them, and a brief description of how the virtual workshop would be run. Once an RSVP had been received and attendance confirmed, each stakeholder was sent a copy of a briefing document (Appendix L) to read in anticipation of the workshop. The PWH stakeholders were reimbursed for their time.

5.10.2 Briefing Document/ Needs analysis

In keeping with the recommendation by O'Cathain and colleagues (195) , and reflecting elements of a model for complex intervention development for nursing (323), multiple sources were synthesised into an analysis of need for the development of this theory. The background evidence base (detailed in Chapters 1, 3 and 4) including published guidelines and reviews were collated, and with the knowledge and experience of the wider clinical academic team were assimilated to create a briefing document for use by the stakeholders. Participants were asked to read this document before the meeting, to formulate their own views and opinions of the document and consider how it could help inform the ToC process. The document also included a broad overview of the concept of building a ToC.

5.10.3 Online interactive group

Stakeholder workshops for a ToC process are usually in person which allow for a high level of interaction to conceptualise, organise, and agree ideas that ToC is associated with. However, due to the ongoing COVID-19 restrictions regarding face-to-face meetings at the time, the decision was taken to arrange an online virtual workshop. To try and create as open and interactive a session as possible, an online platform called Padlet® was used (www.padlet.com). Padlet is a real time, collaborative platform that functions like a digital notice board. It does not require sign up from users and is free to download and use. Users can create walls upon which 'sticky notes' can be added, and it also supports other file types such as pdfs, word documents and pictures. These

notes can then be moved, removed, and edited as group discussions progress. It also allows the notes to be colour coded, connected, and organised into themes and processes. The researcher was the meeting host as well as facilitator using the Zoom® videoconferencing platform, screen-sharing a blank Padlet screen with all of the participants. This allowed all participant webcams to be visible which helped to enhance social connectedness in the meeting. The researcher took the position of 'critical friend' throughout, facilitating the workshop objectives, but ensuring that issues and discussion generated was led at all times by the stakeholders. One of the researcher's supervisors (DS) also attended the workshop as second facilitator/observer. All the content created for the notes was informed by the stakeholders' discussions and agreed as important to be included. The workshop was planned to be no longer than three hours, including a break midway.

5.10.4 Building the programme theory

All participants were asked to give a short introduction about themselves to the group, and a short icebreaker was included to relax attendees into the workshop. This stakeholder-led approach to theory development requires those attending to first identify and agree what the overall aim/ long term change needed for this intervention would be, i.e., the end point. From this point the group 'worked backwards' identifying the medium and short terms outcomes, the pathways needed to achieve the outcomes, as well as the people, places and contextual issues involved at each stage. The overall discussion points were focussed on the exercise-based intervention delivery, content, logistics and the education component. Participants were encouraged at all times to be mindful of the transparency of proposed causal attributions as well as be realistic in how their suggestions would be done in the real-world setting. The researcher typed up the notes as participants discussed them, making sure that queries were addressed about accuracy and meaning if it was unclear when notes were being made. Although discussions occasionally focussed on very person specific activities, participants were encouraged to keep looking and thinking at processes to enable the change they wanted to see in the intervention, the 'how and why' rather than just the 'what.' Enablers and barriers to processes and change were identified and discussed in the context of the short and medium-term outcomes. Many of these were also highlighted and identified in the data informing the briefing

document preceding this meeting and were added to the model. Time points and context of activities and strategies for this feasibility study development were also discussed and added to the map.

At the end of the workshop participants agreed the discussions had been thought provoking and fruitful, producing a lot of information that was broadly in an order that made sense to them and the context of the study at hand. In the week following the workshop the researcher used the Padlet walls that were created to inform the construction of a visual ToC framework and an accompanying narrative report.

5.10.5 Mapping COM-B to the Theory of Change map

The initial behavioural analysis was established from the same evidence base and needs analysis as that used in the ToC. The behaviour that needed to change was the limited use of exercise (at home or in haemophilia clinics) for people with severe haemophilia who reported living with chronic joint pain.

A behavioural diagnosis was then completed using the COM-B behavioural diagnosis form. From this diagnosis, the findings from the qualitative study described in Chapter 4, as well as the output of the stakeholder informed ToC was mapped against the COM-B model and the relevant intervention functions identified. Specific BCT's were then chosen from the BCT Taxonomy (322) and linked to these intervention functions, targeting potential mechanisms of change to include and evaluate within the feasibility study.

5.11 Results

Three PWH and two specialist haemophilia physiotherapists volunteered and agreed to participate in the ToC workshop. The researcher was the facilitator of the Zoom-hosted workshop, held on the 4th November 2020. One academic supervisor (DS) also attended. The workshop was recorded (with permission) and lasted 3 hours. Two Padlet walls with notes were produced from the discussions in the group. Examples of these can be found in Appendix M.

Using the notes from the workshop, the Padlet walls, and the audio recording, the researcher created a ToC visual map that encapsulated the process. The written narrative providing further detail of the content was then sent to the group for review and comments/additions/edits. Within two weeks, all of the group had responded, and

the map was reviewed and edited accordingly. When all of the group had agreed the map and report represented the workshop and the process overall, was it signed off as complete.

5.11.1 The Theory of Change map and narrative report

The final theory of change map is presented below in Figure 24.

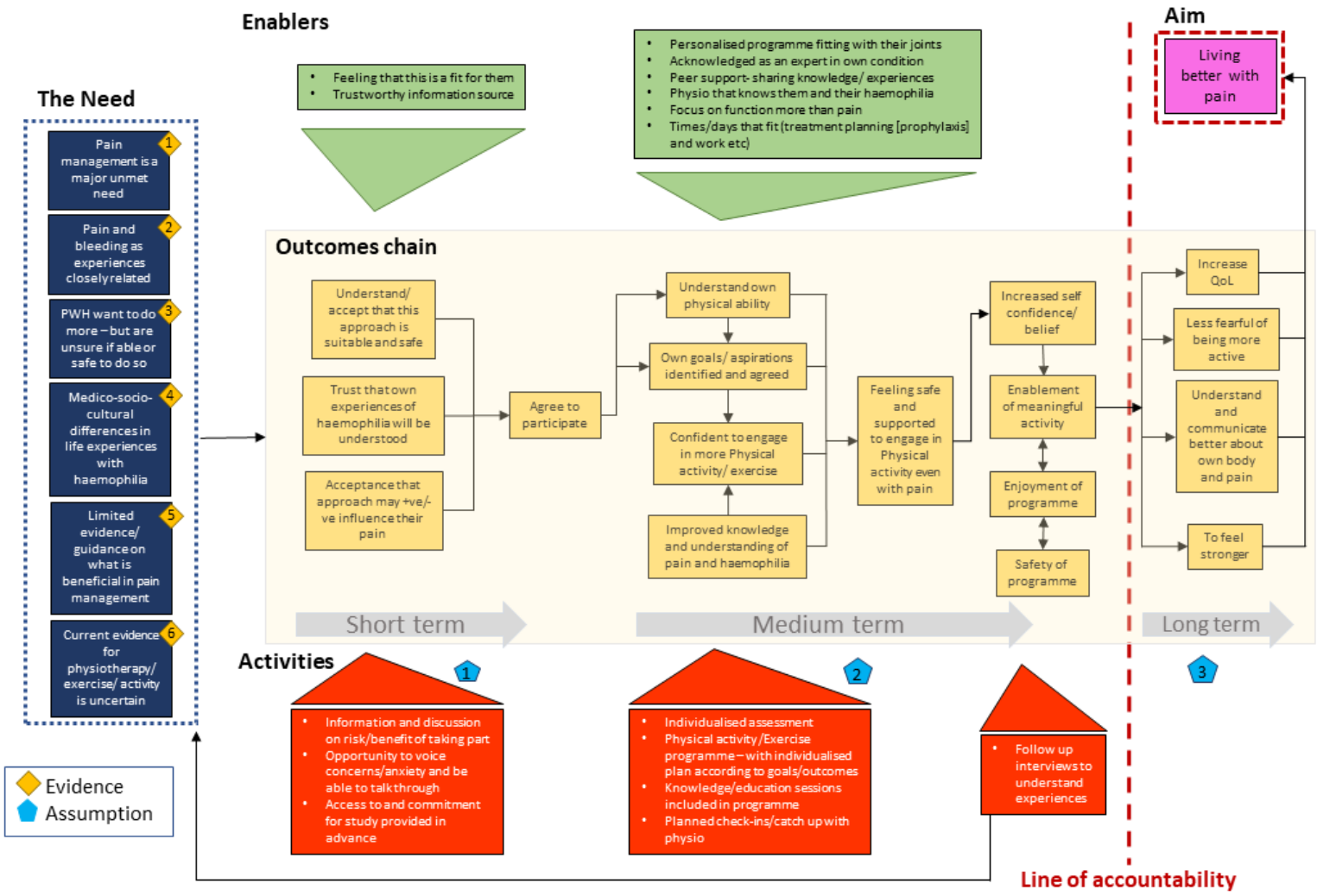


Figure 24: Theory of Change map for the REMAP-Haemophilia study

The overall aim of the intervention described by the stakeholders was 'Living better with pain' and is presented on the top tight hand side of the map. The 'need' for this approach based on the current available evidence, is summarised, and presented on the left of the diagram. The 'outcomes chain' relates to the period of the feasibility study and presents the assumed causal chain of events for a participant to successfully take part in the intervention. The successful progression through the outcomes chain is dependent on the influence of the identified 'enablers' and the inclusion of 'activities' within the intervention itself. The 'line of accountability' highlights the longer-term outcomes that are considered beyond the scope and measurement of the current study. The assumptions and evidence are presented below in Table 10.

Table 10: Evidence base and assumptions included in the Theory of Change map

Assumptions	1. – PWH who have pain attend regular clinical reviews in their haemophilia centre- so will be identifiable as possible participants from there - Physiotherapists will be engaged in the study and willing to undergo training to deliver the intervention. - Information about the study will be delivered by the specialist physiotherapist known to the PWH. 2. – The technology will be available for both PWH and Physiotherapist to participate in this study. - Training will be provided for PWH on using virtual/ remote platforms (as permitted to be used on each site) - Intervention activities will be carried out within normal working hour week (with cost/time of study participation reimbursed to therapy departments - Outcome measures will be selected for the study protocol to reflect information gathered from interviews and this theory of change workshop. 3. The map created here will likely need to change/be adapted following completion of the study – this will be addressed in a follow up Theory of Change meeting.
Evidence	1. Literature review (Chapter 1) 2. Systematic Review (Chapter 3) 3. James Lind Alliance Report (64) 4. Findings from focus groups and interviews (Chapter 4) 5. World Federation Haemophilia Guidelines 2020 (111)

5.11.2 Theory of Change narrative report

5.11.2.1 Context and need

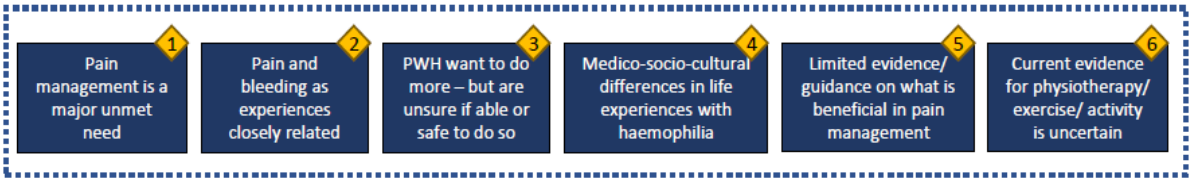


Figure 25: The 'Need' component of the Theory of Change map

Chronic pain associated with haemophilic arthropathy is a pressing clinical and personal issue for many PWH, with figures indicating over 50% of PWH live with chronic, poorly managed pain. Pain has also been highlighted as a top research priority by clinicians and people with bleeding disorders in a recent James Lind Alliance priority setting partnership (64).

The qualitative study in Chapter 4 indicates that pain in PWH is complex due to its close association with bleeding, its lifelong presence, and the difficulties with acute on chronic pain episodes such as those with arthropathy. Fear of bleeding as an initial response to pain has meant that many living with pain feel unwilling to be more physically active in case of further consequences. However, PWH acknowledge they would like to feel more confident and better supported to be more active and functionally well regardless of their pain.

Whilst guidelines relating to pain management in haemophilia relate mostly to pharmacological/drug management, the findings in Chapter 4 suggest PWH are unwilling to take further pain medications and would rather seek out other non-pharmacological options. Although physiotherapy is mentioned in the recent WFH guidelines, its potential role in pain management is poorly defined, resorting to generic advice on functional training (111). The systematic review in Chapter 3 concluded evidence of effect on pain from a wide range of physiotherapeutic interventions is unclear. Pain as an outcome was poorly assessed (using a 0-10 score) and was not associated with functional measures in most of the included studies.

Individual life experiences of haemophilia are varied and depend on age and availability of treatment, country of birth and access to knowledgeable haemophilia healthcare professionals. Such life experiences of healthcare, as well as living and managing with a rare disease, have meant many PWH are experts in their own disease on a day-to-day basis. However, pain management appears to be a complex issue that requires further support and input from clinicians who understand both haemophilia and the individual it is affecting.

The lack of previous work on this topic has meant the intervention being developed and discussed here will be examined within a frame of feasibility – is it safe, can it be done/delivered, and is it acceptable to those taking part in it. Although this approach is novel, it also addresses the issue of geography and distance in haemophilia care being delivered via regional comprehensive care centres. The study will be able to assess if specialist haemophilia physiotherapy can be delivered 'locally' using remote technology.

5.11.2.2 Activities/ strategies

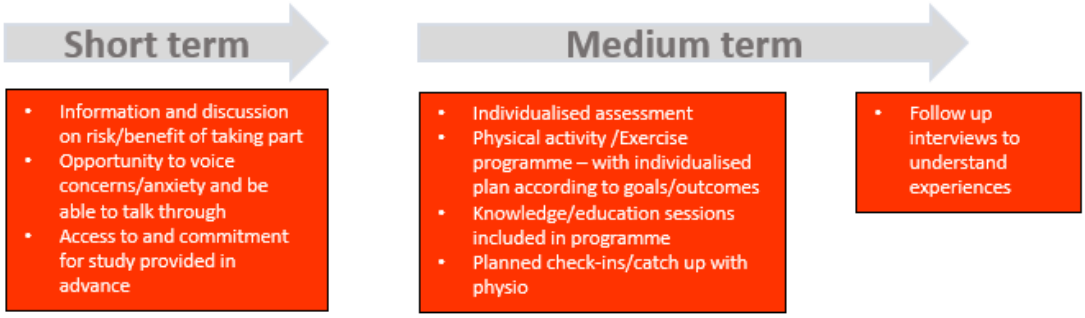


Figure 26: The 'Activities' component of Theory of Change map

A major determinant for successful implementation of the intervention study will be to manage an individual's initial fear and anxiety around such an approach and to embed an engaging 'sales pitch' as part of the recruitment. A recurring theme highlighted by stakeholders was the importance of acknowledging the variance of joints affected by haemophilic arthropathy across possible participants. This selling point would be to describe the activities included in the protocol and to provide reassurance on its appropriateness for someone like them with haemophilia. This upfront discussion allows individuals to have

detail about the time requirement and how it will be able to fit with their individual prophylaxis regimes, as well as confirmation that it will be conducted by someone who knows and understands them and their situation. Individualised assessment and development of a personalised programme will be a key component of participation. It will be completed by their own specialist physiotherapist and discussions around short term goals and outcomes will be central to meaningful engagement and overall outcome assessment at the study completion.

A focus on increasing physical activity levels and meaningful physical function, of which 'exercise' can be part, was felt to be more acceptable to PWH, whilst still being able to capture and engage those with a wide spectrum of physical ability, pain, and joint disease. Number of sessions rather than number of weeks will permit potential participants to have a 'bad day' and choose not to be able to participate, but still engage in the same number of sessions overall. Sessions will have a core element of cardiovascular activity and functional strengthening. Approaches such as High Intensity Interval Training (HIIT) were suggested, as the short burst nature of its application can work well for those easily fatigued and with joint pain issues. However, agreement was made to use intervals but with low impact, moderate intensity activity. This was felt to be more appropriate for all fitness and joint health levels. The programme will accommodate progression of activity over the duration of the study. Regular check-ins and reviews will help engagement, allow for queries to be answered and highlighting improvements to participants. These sessions will be one to one and delivered virtually over whichever virtual platform is available in haemophilia centres.

Participants will record their experience of the activity on a weekly diary, as a visual review of their own achievements as well as a data collection method for the study.

Knowledge and education sessions will be interspersed throughout the programme. These will focus on understanding joint health in relation to bleeding, arthritis, and pain, as well as information about the benefits and safety of physical activity even with haemophilia and arthritic pain. This was proposed as a way of enabling PWH to be able to understand and reason better about their own pain experiences, regaining control over their pain limited activity and being more confident in their decisions to be active with pain.

The physical activity sessions and knowledge/education session will be delivered by a trusted source, the individuals own physiotherapist.

In keeping with a feasibility study design, participants and the physiotherapists who delivered the programme will be interviewed after the study is completed to collect information about their experiences of participating in the study. This information, along with the overall results of this study will be used in the follow up ToC meeting. This will review the current map, and discuss what needs to change in the process map for further development of the intervention.

5.11.2.3 Enablers

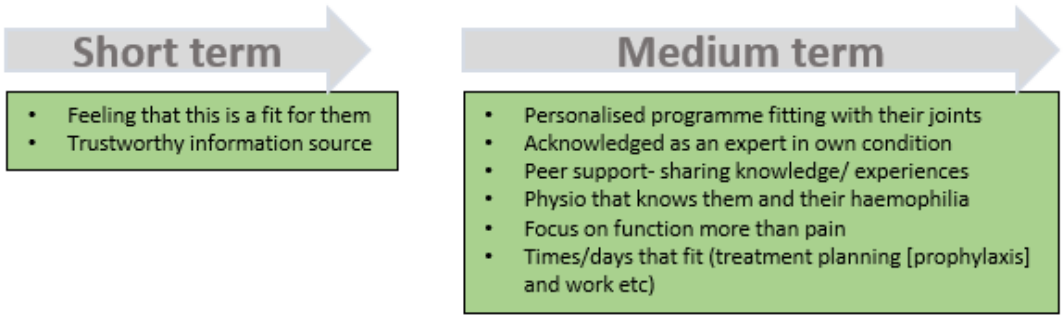


Figure 27: The 'Enablers' component of Theory of Change map

Successful impact on the outcomes chain from the activities will be influenced by identification of both enabling factors and barriers to implementation. The following section focuses on the enablers that have been discussed in the ToC workshop, as well as those voiced by individuals who took part in the interviews and groups earlier in this process.

It is important that PWH feel that they 'belong' in an approach that uses physical activity and exercise as an intervention. This is embedded in the lived history of their experiences of activity, bleeding, and pain, as well as what they have been advised growing up about exercise (i.e., possibly dangerous). Conversations and discussions about participating in this type of study need to be held with people they trust and know, such as a known and trusted haemophilia specialist physiotherapist. This therapeutic relationship also means participants are happy and willing to have follow-ups and check-ins as needed about their

progress, enabling trust to continue in the study and positively influencing motivation and engagement.

People with haemophilia need to be acknowledged as experts in the day-to-day management of their condition and for this to play an active role in conversations around goals and outcomes of participating in a study like this. An individual assessment and personalised plan to use in the study will facilitate engagement and allow positive discussions around why this kind of intervention will be ok for them to do.

The focus of the intervention needs to be on better day-to-day function more than just measuring pain. This will help people focus on things they feel they can change, as pain is something they have lived with for a long time, and resolution of it is not something to expect with an intervention like this.

Worries about the possibility of bleeding due to being more active can be managed if the time commitment, days and times of sessions are known in advance and prophylaxis treatment schedules instigated. Having confidence in a high circulating factor level (when pain is present) allows people to be less concerned about 'bleed pain' and focus more on arthritic pain, which is viewed as less threatening. Planning for participation is important so that it can also be accommodated into the working day, as many PWH are of working age.

Anxiety over negative body image and worries of feeling intimidated about doing exercise activity will be minimised by doing it in a virtual 1:1 session. However, having an opportunity to share thoughts and experiences with others in the study is a positive element of the intervention, which will bring the benefit of social connection and discussing shared-experiences and strategies that others have used and can use. Feeling part of a group in this way may also increase motivation to continue with the programme by fostering a sense of shared identity and experience.

5.11.2.4 Desired results (outcomes chain)

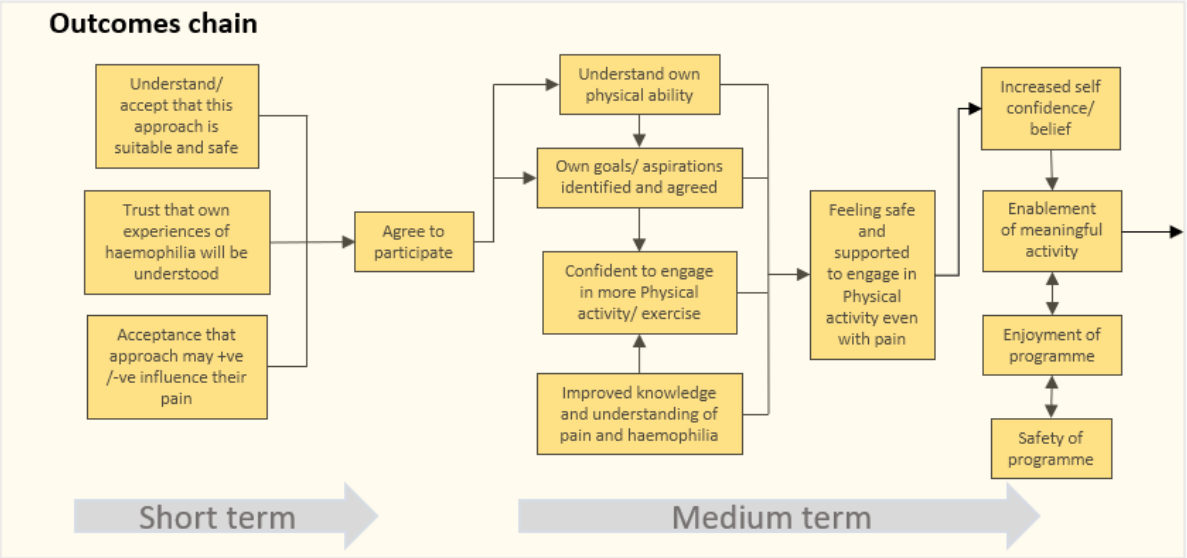


Figure 28: The 'Outcomes chain' component of Theory of Change map

The outcomes chain identifies outcomes across the short and medium time frame, with interconnectedness between outcomes highlighted by directional connecting arrows. The outcomes presented here apply only to the PWH who agree to take part in the intervention.

The short-term outcomes relate to study recruitment, and demonstrate the consequence of the personalised and highly informative process in getting people to consider participating in the study. Improved understanding of why and how a programme like this may be beneficial for them will facilitate a process of well-informed internal reasoning resulting in agreement to participate.

The medium-term outcomes relate to active participation in, and delivery of, a physiotherapy led programme of exercise that focusses primarily on functional improvement and pain as a secondary outcome. It highlights how feeling safe and confident to engage in physical activity with pain present is influenced by individualised physical capabilities of fitness and strength, as well as enhanced knowledge and understanding of pain and arthropathy that relates to them and their life experience. An improvement in self-belief, improving physical ability, experiencing the safety of the intervention and enjoyment of the programme leads to further participation in activities that matter to them outside of the study activity.

5.11.2.5 The line of accountability

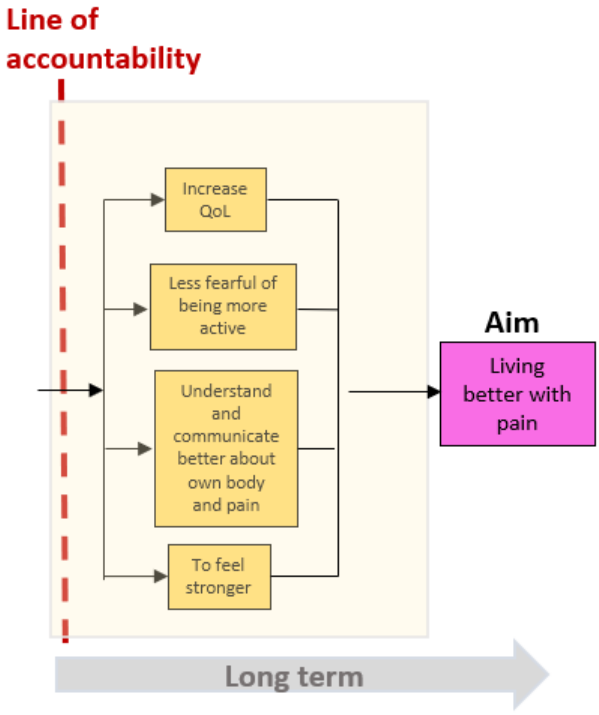


Figure 29: The 'Line of accountability' component of Theory of Change map

At the "line of accountability" on the ToC map it cannot be implied that the intervention described is driving change in long term outcomes anymore. The proposed intervention applicable here aims to see if PWH will participate in this intervention, if it is acceptable and safe for then to do so, and if activities in the study have any short- to medium-term effect on self-identified outcomes relating to physical function and day to day pain. It is unclear if longer term health benefits can be achieved with this study approach alone. However, post intervention analysis of both qualitative and quantitative data will help inform the success of this feasibility study and will be used to develop the next stage of further studies.

5.11.3 Mapping COM-B to the theory of change map

The behavioural analysis focussed on how to engage PWH with chronic pain to take part in an exercise intervention delivered virtually by their specialist physiotherapist. A behavioural diagnosis was completed using the COM-B behaviour diagnosis form (Table 11). This clarified and quantified the specific details for mapping to the COM-B and helped identify the intervention functions of interest (Tables 12 and 13). These intervention functions then identified 21 BCT's to be included in the design of the REMAP-Haemophilia study protocol (Figure 30). These BCT's are detailed in Table 14 and listed according to their corresponding number in the BCT Taxonomy (322).

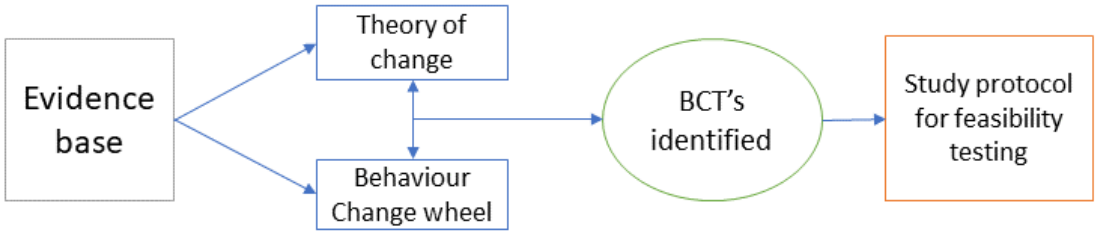


Figure 30: Schematic of mapping the theory of change to the Behaviour change wheel and COM-B

Table 11: COM-B Behavioural Diagnosis Form – Participating in REMAP Haemophilia feasibility trial

CAPABILITY		
1.	Know more about why it was important	Potential benefits of exercise and activity for pain management What and why they have pain
2.	Know more about how to do it	What exercises and how to do it How to get online for the exercise class
3.	Have better physical skills	How to use the technology associated with online sessions Be able to set up a home exercise spot
4.	Have better mental skills	How to reason and monitor the possible increase in pain during or after exercise
5.	Have more physical strength	How to build up from a baseline of poor physical strength
6.	Have more mental strength	Develop stronger resilience against stopping activities due to worry – being more confident and trusting in own ability as well as person leading the exercise
7.	Overcome physical limitations	How to get a work around of exercise and activities to fit in with joint damage and limitations
8.	Overcome mental obstacles	Reduce unwanted feelings of fear and worry over exercise
9.	Have more physical stamina	Develop a greater capacity to maintain the physical effort required to take part comfortably in a 20-30 min exercise class twice a week
10.	Have more mental stamina	Develop greater capacity to maintain mental effort: concentrate and follow both the exercise and discussion sessions
OPPORTUNITY		
11.	Have more time to do it	Creating a dedicated time at least once in the week (max twice) to be able to take part in the study
12.	Have more money	Having money to own/buy webcam enabled device
13.	Have the necessary materials	Have access to all the necessary equipment that may be needed to be able to do the home exercise programme including webcam
14.	Have it more easily accessible	Be able to have private space/facilities to do the study
15.	Have more people around them doing it	Being part of a group also taking part in the study
16.	Have more triggers to prompt them	Emailed or texted reminders about the exercise sessions
17.	Have more support from others	Encouraged to discuss their participation in the study with family and friends so that they understand its purpose as well as being able to offer support and encouragement
MOTIVATION		
18.	Feel that they want to do it enough	Feel a sense of pleasure or satisfaction from taking part in the study
19.	Feel that they need to do it enough	Care about the negative consequences of not doing the trial – this maybe guilt (for group), that they miss the feeling of betterment after the exercise, wanting to do it so they see what happens at the end

		Use of outcomes identified by them as an enabler of participation and change
20.	Believe that it would be a good thing to do	Need to have a stronger sense that it is a good thing to do
21.	Develop a better plan for doing it	Clear and developed plan of taking part – timetabled firm times as well as when check in points will be, the end points, follow up and what is expected
22.	Develop a habit of doing it	Getting into the pattern of doing the exercises Embed dates and times in their weekly routine
23.	Something else (specify)	N/A

Table 12: COM-B domains and REMAP-haemophilia study – Links to Intervention Functions

COM-B	REMAP-Haemophilia	INTERVENTION FUNCTIONS
Physical capability	How to use the technology at home associated with online exercise classes How to build up from a baseline of poor physical strength	Training
Psychological capability	Knowledge of their haemophilia/pain relationship – and relationship with own individual exercise plan	Education
	Knowing how to use computer correctly/ digital literacy Knowing how to do their exercises and when and how to ask for help and advice Knowing how to progress their exercises when they feel able	Training
	Remembering to attend and be present within sessions Asking for help/advice in good time Having an escalation plan to consult if things are difficult	Training Environmental restructuring Enablement
	Method of recording what it has been done and check for progress Confidence in choosing to do exercise even if non-bleed joint pain present Monitoring for symptoms on that day and the day following	Education Training Modelling Enablement
Reflective motivation	Identity - is it OK for someone with severe haemophilia and associated pain to be taking part in exercise	Education Persuasion Modelling
	Confidence that exercise for pain management something that they can do with joint disease, pain, and haemophilia Participant confidence that this study is ok to do (i.e., not dangerous and may have a positive effect)	Education Persuasion Modelling Enablement

	Understand the knowns and unknowns of the study – and what do they think is the worst what can happen	Education Persuasion Modelling
	Recognise personal readiness to take part in this study How much to they want to do and are they prepared to change?	Education Persuasion Incentivisation Coercion Modelling
Automatic Motivation	What are the incentives to want to participate?	Training Incentivisation Coercion Environmental Restructuring
	Understand potential fears of exercise, fear of bleeding and fears of consequence of exercise on more pain and effect on work and mobility	Persuasion Incentivisation Coercion Modelling Enablement
Physical opportunity	PWH stated that was effort of time and distance in coming to hospital for a rehabilitation intervention – potential benefits of home-based virtual participation Trusted source is very important	Training Restriction Environmental restructuring Enablement
Social opportunity	What do their friends and family think about being more active and the risk of more pain (in the short term) Is a group session acceptable	Restriction Environmental restructuring Modelling Enablement

5.11.4 Identification of BCT's for inclusion in feasibility study protocol

Table 13: Intervention function links to BCTs identified for REMAP-Haemophilia study

Intervention Function (and Definition)	**COM-B components served by intervention functions**	**BCTs identified**	**Intervention strategy in REMAP-Haem study.**
Education (Increasing knowledge or understanding)	Psychological capability Reflective Motivation	5.1- Information about health consequences 2.2- Feedback on behaviour 2.3- Self-monitoring of behaviour	Providing information about joint damage and pain in haemophilia Information on benefits of physical activity/exercise Feedback by physiotherapists at end of each week's activity – a recap of what was achieved Weekly reflective diary on own activity and pain
Persuasion (Using communication to induce positive or negative feelings or stimulate action)	Reflective Motivation Automatic Motivation	9.1- Credible Source 5.1- Information about Health consequences 5.4 – Monitoring of emotional consequences 2.2- Feedback on Behaviour 2.7- Feedback on outcomes of the behaviour	Intervention will be delivered by expert haemophilia physiotherapist, known to the participant Providing information on joint damage and pain in haemophilia Information on benefits of physical activity/exercise Encouraged to feedback with worries and fears over what they are feeling whilst taking part in study (focus on pain and activity) – weekly diary Feedback by physiotherapist at end of each week's activity – a recap of what was achieved Feedback at study end of before and after results of measures Interviews with participants
Training	Physical Capability	6.1- Demonstration of the behaviour	Each exercise set and start point will be agreed upon at initial visit with explanation and practice demonstration within boundaries of individual ability.

(Imparting Skills)	Psychological Capability Automatic Motivation Physical Opportunity	4.1- Instruction on how to perform a behaviour 2.2- Feedback on behaviour 2.7- Feedback on outcomes of Behaviour 2.3- Self-monitoring of behaviour	Physiotherapist will demonstrate each new exercise within the session before each set Participants will be issued with exercise list – as well as set up instructions for webcam visuals, plus using diary Feedback by physiotherapist at end of each week's activity – a recap of what was achieved Feedback at study end of before and after results of measures Weekly reflective diary on own activity and pain – to include Rated Perceived Exertion (RPE) scale with activity each week
Environmental restructuring (Changing the physical or social context)	Psychological capability Automatic Motivation Physical Opportunity Social Opportunity	12.5- Adding objects to the environment 7.1- Prompts/cues 12.1- Restructuring the physical environment	Provision of list of exercises booklet explanation, Thera-band and paper diaries and RPE Laminated RPE scale next to webcam so can look and answer the physiotherapist when asked about this in activity session. Encouraged to create a place of quiet for them to do their exercise session – and where they can have their phone or laptop/webcam so as to be able to take part with best view for all
Enablement (Increasing means/ reducing barriers to increase capability (beyond education and training) or	Psychological capability Reflective Motivation Automatic Motivation Physical Opportunity Social Opportunity	3.2- Social support (practical) 1.1- Goal setting (behaviour) 1.3- Goal setting (outcome)	Participant partner/family/neighbour will be used if necessary to help in setting up the webcam if necessary – as well as being someone to call upon if any issues such as risk of falls etc. -Overarching goal is for participants to participate in a virtual online exercise session twice a week -Sub goals based on self-identified activities of choice -To be more willing to be more active (even with pain) at the end of the study

opportunity (beyond environmental restructuring).		12.5- Adding objects to the environment	-Provision of exercise list, Thera-band, and paper diaries and RPE scale
		1.2- Problem solving	Identify potential barriers to taking part in the study. Generate individualised solutions to help ameliorate/overcome barrier – this can be iterative process as intervention proceeds. Knowledge and discussion sessions can be used to work through barriers or negative emotions/thoughts in respect of rehab activity
		1.4- Action planning	Frequency and intensity of intervention determined from initial face to face session Intervention sessions planned in accordance with established prophylaxis regime (safety planning) Discuss with each participant what their trough levels would be the day following prophylaxis (enable reasoned process if pain worse and fear of bleed). Permission/encouragement to wear splints, supports etc if they feel they need to
		2.3- Self-monitoring of the behaviour	Weekly reflective diary on own activity and pain – to include RPE scale with activity each week
		12.1- Restructuring the physical environment	Encouraged to create a place of quiet for them to do exercise session – and where they can have their phone or laptop/webcam so as to be able to take part with best view for all
		1.5- Review behaviour goal(s)	Weekly review of attendance and participation in intervention – amend/revisit initial goals setting if newly identified issues
		8.7- Graded Tasks	Exercise activity has graded allowances built-in (more reps, harder/easier effort level) – and will be increased weekly depending on performance
		15.1- Verbal persuasion about capability	Positive reinforcement following initial face to face assessment as intervention will be delivered in accordance to their abilities and by a physiotherapist who understands them and their ability

			Each person to have a very individualised programme of exercise that recognises their own specific HA joints
		9.2 Pros and Cons	Discussions in initial session to encourage individual to identify pro's and con's of taking part in study – which are noted in the individuals paperwork and discussed with physiotherapist. Pros and Cons to be addressed in qualitative study for feasibility
		13.2- Framing/ Re-framing	Suggest participants view intervention as a physical activity enabler rather than changing their pain

Table 14:List of Behaviour Change techniques included in REMAP-Haemophilia study

BCT Label and taxonomy number	Intervention component
1.1 – Goal setting (behaviour)	For participants to participate in a virtual online exercise session twice a week. Sub goals based on self-identified activities of choice
1.2 – Problem Solving	Identify potential barriers to taking part in the study and generate individualised solutions to help overcome barrier – can be iterative process as intervention proceeds. Group knowledge and discussion sessions used to work through barriers or negative emotions/thoughts in respect of activity.
1.3 – Goal setting (outcome)	To be more willing to be more active (even with pain) at the end of the study
1.4 – Action Planning	Intensity of intervention determined from initial visit with physiotherapist. Sessions planned in accordance with established prophylaxis regime (safety planning). Discuss with each participant what their trough levels would be the day after prophylaxis (enable reasoned process if pain worse and fear of bleed). Encouragement to wear splints, supports etc if they feel they need to.
1.5 – Review behaviour goal(s)	Weekly review of attendance and participation in intervention – amend/revisit initial goals setting if newly identified issues
2.2 – Feedback on behaviour	Feedback and recap by physiotherapist at end of each week's activity
2.3 – Self monitoring of behaviour	Weekly reflective diary on own activity and pain – to include RPE scale with activity each week
2.7 – Feedback on outcomes of behaviour	Feedback at study end of before and after results of outcome measures
3.2 – Social support (practical)	Participant partner/family/neighbour will be used if necessary to help in setting up the webcam if necessary – as well as being someone to call upon if any issues such as risk of falls etc.
4.1 – Instruction on how to perform behaviour	Participants will have practice session for exercises on their list – as well as set up instructions for webcam visuals, plus using diary
5.1 – Information about health consequences	Providing information on joint damage and pain in haemophilia and benefits of physical activity/exercise.
5.4 – Monitoring of emotional consequences	Encouraged to discuss worries/fears whilst taking part in study (focus on pain and activity) and weekly diary
6.1 – Demonstration of the behaviour	Each exercise set and start point will be agreed upon at initial visit with explanation and practice demonstration within boundaries of individual ability. Physiotherapist will demonstrate each exercise within the session before each set.
7.1 – Prompts and cues	Laminated RPE scale next to webcam so can look and answer physiotherapist when asked about this in activity session.
8.7 – Graded tasks	Exercise activity has graded allowances built-in (more reps, harder/easier effort level) – and will be increased weekly depending on performance
9.1 – Credible Source	Intervention will be delivered by expert haemophilia physiotherapist, known to the participant
9.2 – Pros and cons	Discussions in initial visit to encourage individual to identify pro's and con's to taking part in this study – which are noted in the individual case report form and discussed with physiotherapist.
12.1 – Restructuring the physical environment	Encouraged to create a place of quiet for them to do their exercise session – and where they can have their laptop/tablet webcam so as to be able to take part with best view for all.
12.5 – Adding objects to the environment	Thera-band and paper diaries and RPE scale
13.2 – Framing/ Reframing	Suggest participants view intervention as a physical activity enabler rather than changing their pain
15.1 – Verbal persuasion about capability	Positive reinforcement following initial assessment visit and in all sessions - intervention will be delivered in accordance to their abilities.

5.11.5 The REMAP-Haemophilia Study

An overview of the final REMAP-Haemophilia intervention is presented in Figure 31.

The methods for the study are described in detail in Chapter 6.

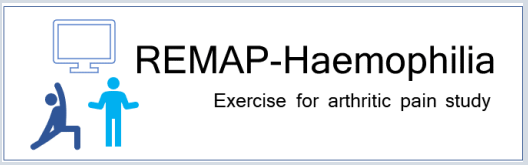
REhabilitation for the **M**anagement of **A**rthritic **P**ain in Haemophilia: The REMAP-Haemophilia study 	
STUDY DESIGN	Multi-site, non-randomised, pre-post feasibility with exploratory nested qualitative study
STUDY SETTING	Haemophilia comprehensive care centres in England
CONTENT	1 face to face session 2 exercise sessions per week over 6 weeks: - Low impact, moderate intensity targeting both upper and lower limbs 3 Knowledge and discussion sessions - Weeks 1, 3, and 5 Embedded behaviour change techniques in study design and delivery Post participation interviews – PWH and physiotherapists
FORMAT	1 x in-person session: completion of outcome measures, practice exercises 1 x dry-run with participants of using webcam for exercise in own home 6 x individual and 6 group exercise sessions – real-time, virtual delivery 3 x knowledge and discussion sessions – real-time, virtual delivery Post participation interviews – telephone or video-conferencing platform
RESOURCES	Staff: specialist haemophilia physiotherapist Hardware: Wi-Fi, webcam on computer/ tablet/ telephone Software: Video-conferencing platform Equipment: Resistance exercise bands Other: Confirmed time in diary to run/attend sessions
OUTCOMES	Participant reported, paper based questionnaires: Pain: Brief Pain Inventory and Pain self-efficacy Function: Haemophilia Activities List and Patient Specific Functional Score Quality of Life: EQ5D-5L and Musculoskeletal Health Questionnaire Self-reporting change: Patient Global Impression of Change Experience of taking part: Individual Interviews (participants and physiotherapists)

Figure 31: Overview of the REMAP-Haemophilia study

5.12 Discussion

The MRC framework for developing complex interventions brings focus on the need to understand and explicate what the active components are within an intervention, with theory development and context considered core elements (196). In keeping with this framework this chapter presents how the identification and review of the published evidence base (Chapter 1 and 3), along with an understanding of the contextual issues around pain and exercise for PWH (Chapter 4) have been successfully integrated into synthesising a stakeholder informed theory of change for the development of a complex rehabilitation intervention. The resultant outcomes chain logic model is visually coherent. With the further additional mapping of behaviour change theory to it, the stakeholders consider the theory to be plausible, credible and testable.

Complex interventions involve a number of interacting components that may require new behaviours by those receiving the intervention, or those who deliver it (195). They may also have outcomes that are intended, unintended and multiple, and have implementation chains that can be long and convoluted (324). It is this potential multitude and interlinking of known and unknown variables that creates the concept of the 'black box' in complex interventions, not just 'what' and 'where', but 'why' and 'how' observed effects may be taking place (192). Deeper understanding helps evaluate the significance and applicability of findings, determining if it is the best intervention possible given the differing contexts and constraints in delivery (306). It is the need to understand and better explain this black box that makes the modelling of a complex intervention so important. Living with severe haemophilia brings with it a complex medical regime needed to manage it, widespread musculoskeletal consequences of joint haemarthroses and the lived experience and beliefs of each individual. Acknowledging these multiple factors and the need to understand the degree of interplay between them, confirms that an exercise-based telerehabilitation intervention for PWH living with chronic pain can be considered a complex intervention.

Theory is a set of interrelated concepts and definitions that explain or predict events by specifying relationships between variables (325). The 'black box' of a complex intervention is full of multiple potential theories that need to be made explicit to permit understanding of the intervention (192). Where no previous theoretical

approach is appropriate or available to use, an intervention specific theory needs to be created, therefore a theory of change approach was used here to conceptualise a testable theory. The collaborative approach used here privileges the personal expertise and lived experiences of stakeholders alongside the current evidence base, thus making clear the needs being addressed, the outcomes to be achieved and the activities planned (318). De Silva and colleagues were the first to suggest how the use of this approach could positively complement the MRC framework (316). The method provides a frame for theory in the development phase. Being sited in real world context and with stakeholder consensus in the content, means realistic expectations of the intervention are established. In the feasibility phase, a theory of change can improve testing by providing early evidence of links between the project activity and short-term outcomes. This helps to highlight barriers to implementation and refine the intervention.

By virtue of its status as a rare disorder and acknowledging the multi-faceted impacts on daily life living with haemophilia, the potential for research time and effort wasted on potentially low value interventions needs to be avoided. The findings of Chapter 3 highlight that PWH are interested in finding ways to help manage their pain better and they want to be involved, listened to, and have their wants and needs incorporated into their management. To date no rehabilitation study in haemophilia has previously clarified the development of a theoretical underpinning to those interventions being evaluated, so this chapter is the first time the ToC approach has been used with PWH. The positive experience of those taking part provides initial groundwork for this approach to be further developed.

Stakeholder engagement is a core element of the MRC framework in complex intervention development. Involvement of stakeholders from the outset is vital, as they understand the problem at hand and can identify the priorities in order to find realistic, workable and meaningful solutions (195). Engaging with stakeholders requires shared commitment and understanding, with a clear process of how input will be gathered and used (326). Yardley et al described three examples of using a person based approach to enhance feasibility and acceptability of behaviour change interventions for people with asthma and diabetes (327). The examples ranged from stakeholders informing the design of a web-based intervention using findings from

both quantitative and qualitative literature, to a 'Think aloud' process to refine patient information leaflets. In extoling the benefits of the approaches, they highlight the need to acknowledge the potential for friction between researcher and stakeholder views, and the difficult decisions research teams may have to take when modifying interventions. However, such productive conflicts can often result in useful negotiation and ultimately bring substantial benefits by ensuring culturally and logistically appropriate research (328).

Whilst there is little evidence in the current literature pertaining to involvement of PWH for intervention theory development, there have been other successful examples of participatory approaches in developing methods to improve haemophilia care delivery. A novel goal-oriented outcome measure informed by previous qualitative research, the GOAL-Hem, was created by researchers (329). Only after it had been feasibility tested were patients and carers were then invited to review, evaluate, and feedback on the language used as well as the usefulness of each goal. They reported that PWH became more enthusiastic for the tool because of their participation in this process. Whilst the involvement of stakeholders was beneficial, it is likely that earlier involvement in the design of the measure, including the content and language used may have streamlined the process and enabled stakeholder sense of value and ownership earlier. In contrast, a pain treatment planning questionnaire was conceptualised with patients and carers being involved from the start. The tool was developed in partnership; patients were interviewed to guide and inform the content, which was then further refined after clinical testing using a 'Think aloud' approach. The authors noted that the co-design approach was instrumental in developing the condition specific checklist within the questionnaire that was also acceptable for the patient population it was tested on (118).

Another recent study by Timmer and colleagues worked with stakeholders (PWH and primary care physiotherapists) to explore their experiences of primary care and develop recommendations to optimise physiotherapy care co-ordination (330). In approaching this problem this way, they were able to get consensus on 13 recommendations for better physiotherapy care that may improve service quality and reduce waste. They noted that they gained more in-depth understanding of the issues at hand because of their inclusive approach with stakeholders. With the scale of

potential benefits when inclusive stakeholder approaches are used, it is unfortunate there is little current evidence of such approaches being used to develop rehabilitation interventions for PWH.

A programme theory describes how an intervention is expected to lead to its effects and under what conditions, and should articulate the key components and how they interact, and the relationship between the contextual influences and the mechanisms of interaction (196). Rather than a more linear logic model, the outcomes chain diagram in a ToC places more focus on the causality through which the order of the activities is linked, thereby clearly identifying outcomes critical to success (318). It is the rationale and examinations of theory of change maps, with a focus on articulating the outcomes, that takes the ToC into the realms of programme theory (331). Outcome measures represent only one aspect of physiotherapy care, with the focus being on evaluation of practice and less so on factors that may explain why a programme benefits some but not others.

A well-articulated programme theory may optimise practice and provide accountability and efficiency for chosen interventions (332). The ToC map created here identified that a trusting therapeutic relationship was key to accepting that this approach may be helpful in the overall delivery of the exercise intervention. The stakeholders were very aware of the different social and physical contexts of potential participants, and as a result agreed the intervention should focus on low impact, whole body movement and activity, rather than be joint/limb specific. In highlighting this activity approach as an enabler, it was felt to be most likely to achieve the medium-term outcomes in confidence, knowledge, participation, and enjoyment of the programme. The experience of the stakeholders helped to drive a focus towards feeling valued, safe, and supported, which were then hypothesised lead to positively influence subsequent behavioural change of actively taking part in the sessions. The degree of proposed relational detail such as that contained within the ToC map, can provide in-depth delivery knowledge and explanations to help appraise the outcomes for those in the study, and is necessary if the intervention needs to be modified for scaling up or used in different locations (333).

For many rehabilitation interventions the mechanism of action is not readily known (334), attributable to the fact that many rehabilitation interventions have valued

testing theory over developing or building theory(335). The integration of behaviour change approaches in physiotherapy research and practice has been identified as a necessity to develop future interventions related to health promotion and wellbeing (336). For any intervention that proposes to change behaviour, the UK National Institute for Health and Care Excellence (NICE) recommends that the content of the intervention is specified, detail is provided about what is done, by whom and in what context and it is clear what underlying theory will be used to make explicit the key causal links between actions and outcomes (337). The findings from chapters 1, 3 and 4 were used by stakeholders to inform and create a ToC map. A behavioural diagnosis was then created using the same evidence review and qualitative findings of experiences, barriers, and facilitators to doing exercise, and mapped to the Behaviour change wheel and the COM-B components. Specific behaviour change interventions identified from the BCT Taxonomy were chosen for inclusion across the whole study process, from participant identification and consent through to aspects of delivery of the intervention itself.

Whilst no studies in haemophilia to date have used this approach of mapping COM-B to qualitative findings, it has been identified as having potential importance in designing meaningful exercise based interventions for those with living with multi-morbidity (338). A clearly documented development process is important to add to a growing body of knowledge about the explicit methods used in developing interventions (339), benefiting an understanding of the implementation as well as being able to examine the generalisability of the techniques used (322). The process of theory building used here has been described in detail at every stage, presenting both the ToC map of causal links alongside the identified BCT's and the accompanying rationale for their inclusion. This level of detail is crucial in being able to evaluate the strengths and weakness of the overall study design which is critical for improving the next stage of study or trial development (334).

5.13 Reflections on stakeholder engagement

The approach to stakeholder participation described here is novel in terms of previous approaches in PWH. With that in mind, it is important to include a reflective evaluation of their involvement in this process, and how their own interests and beliefs may have influenced and impacted the study.

The three PWH who volunteered to take part in this process were also research participants in the qualitative study in Chapter 4. At the end of their interviews/ focus groups they expressed a genuine interest to be contacted for any future associated development work or studies. All the volunteers were white men, although they did have a wide age range and had a large diversity of experiences of haemophilia. One man had grown up in a country with minimal access to factor concentrate and comprehensive care, even when in adulthood. Another grew up with very intermittent and limited experiences of specialist physiotherapy. All of them had lived with pain associated with their haemophilia since childhood, but also had a positive view on the potential benefits of exercise. It was clear that all three men viewed their participation in this project somewhat philanthropically. Whilst it was made clear that being part of the theory of change would offer them no direct benefit, they reported that it was an opportunity to take part in something that might positively influence physiotherapy care provision for other PWH.

The two female physiotherapists who volunteered to be part of the stakeholder group were specialists from large treatment centres who had each worked in haemophilia for more than 10 years. Both had made contact with me to volunteer their time for any projects associated with the development of the PhD, and both reported that this was due to their own clinical interest in pain management. Similar to the PWH stakeholders, the physiotherapists did not expect a direct benefit from participating. They did note a desire to experience being part of an approach such as this, and an awareness that current approaches to pain management for PWH were insufficient.

Both parties shared similar beliefs that pain management could and should be better, and an interest in what potential benefit exercise may have for managing pain associated with haemophilic arthropathy. The approach used in the theory of change

workshop meant that all views were privileged as equal, enabling a safe and supported space for all suggestions to be talked through, and outcomes only reached by group discussion and group consensus. This focus kept the group coherent, and meant that the agreed suggestions had to be sensible and achievable in a real world setting, further adding to the impact of the theory of change model. I moderated the workshop in the capacity as a critical friend. This required me to hold my own council on the discussions between the stakeholders, and position my views on the topics at hand to be no more important than theirs. Whilst I had some initial anxieties about handing over control, on reflection it was liberating, and actually made the outcomes much more meaningful for the people involved and the intervention as a whole.

This approach to stakeholder participation brought many benefits. It strengthened the focus on recruitment and delivery of the proposed telerehabilitation intervention, as well as highlighting which outcomes to evaluate within the study. The real world applicability of the proposed intervention, with a focus on a low impact/moderate intensity approach was probably the most impactful outcome of this process, and one that would likely not have been included without it. The fact that all the participants had a positive viewpoint of exercise as a consideration in chronic pain management could be seen as a potentially positive bias towards this approach. However, as this was the focus of this PhD it was felt to be appropriate, particularly given the positive and negative experiences of exercise reported in the previous qualitative study. In future development work, there may be merit in engaging with stakeholders who hold a less positive view of exercise, and evaluating if this adds value in recruitment across such populations.

5.14 Strengths and limitations

A major strength of this package of work is the transparency in the approach, with each step reflective of that which came before, and that which follows. The degree of detail regarding process means others can replicate it within their own environments, as well as being able to fully evaluate the process undertaken here.

The approach to co-production taken here for the ToC development is novel, but such an approach serves to shift the power dynamic away from the investigator towards stakeholders. The outcome of this has been a detailed, meaningful, and realistic theory

that can be tested in real-world situations. The experiences and input of the stakeholders changed the intervention development for the better, and in doing so created a sense of ownership by them in that process.

Another strength is the clear, logical, informed process by which BCT's were identified to be included in the study protocol. The BCT's selection process can be situated in the synthesis and evaluation of the evidence base, as well as the mapping process onto the ToC co-produced by the stakeholders.

A limitation of this process may be the relatively small number of people involved in the ToC process. It is possible that a potential bias may present as they had all previously participated in the qualitative study presented in Chapter 4. However, given the time and financial constraint associated with this small feasibility study, the size of the stakeholder group was felt to be adequate by the research management team. The ToC process itself was highly reflexive by virtue of the method and the review process of the map itself, thereby increasing transparency in the decisions made.

Another limitation may be that the ToC map itself may be observed by others outside of the process to be lacking detail, or be thought to be missing outcome chains, activities, or enablers. This view is acceptable, but it must be remembered that the process described here is done in such way so as to be transparent and open to change. This iterative ability is what makes this approach advantageous for use in a feasibility study. The ToC process map will be reviewed again by the stakeholders against the findings of the REMAP-Haemophilia study, and any changes will be included for inclusion in future studies.

5.15 Conclusion

The aim of this chapter was to describe the process in which a programme theory would be built to inform the development and refinement of the REMAP-Haemophilia intervention in readiness for testing in a feasibility study. The stakeholders in the theory of change process identified key outcomes within an interlinked causal model that were postulated to improve the credibility, testability, and acceptability of the proposed REMAP-Haemophilia telerehabilitation intervention. Behaviour change interventions were identified and mapped on to the theory map with specific

behaviour change techniques highlighted for inclusion in the intervention. The overall process involved a complex mix of evidence synthesis and evaluation against the requirement to inform a realistic and testable theory to underpin the study protocol. The result is a theory, described in detail, ready to be tested in a feasibility study.

The methods and protocol for the REMAP-Haemophilia study are presented in the next chapter.

Chapter 6 - Feasibility Study Methods

The previous chapters have highlighted the uncertainty of current physiotherapy interventions in relation to pain management options. They have also described how PWH want to be better supported to better self-manage their pain, with a desire for more non-pharmacological options for their pain. The stakeholder informed theory underpins the study protocol developed. This chapter presents the methods used to evaluate the feasibility, acceptability, and preliminary efficacy of a novel telerehabilitation exercise intervention (REMAP-Haemophilia study) for PWH and chronic pain. It details the recruitment and consent procedure, data collection including outcome measures, and the procedures and exercises involved in the REMAP-Haemophilia study.

6.1 Rationale for a feasibility study design

The MRC framework defines clearly the important role of feasibility testing in the development of new complex interventions (196). Exercise and rehabilitation studies present unique challenges as complex interventions, as people may be excluded due complexity of their condition, age, or concerns over safety. However, pilot and feasibility studies are helpful in balancing the inclusion/exclusion criteria against the issues of safety, recruitment and acceptability (340). The risk of research waste is highlighted with issues relating to formulaic design and lack of efficiency in resolving uncertainties in feasibility studies (341). Some of these issues may be attributable to a lack of clarity on defining when a study is a feasibility or pilot study.

The terms pilot and feasibility continue to be used interchangeably with lack of regard to the differences in their purposes and associated methods (342). Some have suggested that it is futile to define meaning between feasibility and pilot studies, instead suggesting that all preliminary work could be described in a catch-all term of feasibility (343). However, the recent MRC framework accepts and is based on the definitions for feasibility and pilot studies put forward by Eldridge and colleagues (342). They define a feasibility study as that which defines if something can be done in the way it was described, as well as if and how the approach should proceed to evaluation in further studies. Defining sample size calculations for further studies from treatment effects in a feasibility study is also not recommended due to the high risk of

bias and imprecision (344). A pilot study is considered a subset of feasibility study. It includes the above definition as well as the fact that it is either a future study, or part of a future study but conducted on a smaller scale.

The MRC framework is explicit in the requirement of feasibility studies to assess predefined progression criteria relating to both evaluation of the study design as well as the intervention itself. Evaluation of study design should inform the uncertainty around recruitment, defined criteria on success of data collection, retention, outcomes, and analysis. Criteria relating to the intervention should include optimal content and delivery, acceptability and adherence and capacity of the providers to deliver the intervention (196).

Prior to Covid-19, the use of a telemedicine approach was being highlighted as an opportunity for specialist haemophilia care to be delivered locally to those living large distances from their specialist centres (345). Telemedicine approaches for multiple aspects of haemophilia healthcare delivery have been shown to be acceptable to PWH throughout the Covid pandemic (346). Whilst most reports have related to the delivery of routine medical care e.g. clinical review appointments over the telephone or on webcam, others have shown tentative feasibility in delivery of ongoing physiotherapy interventions such as general exercise classes (347, 348) .

In the development phase prior to this study (Chapters 1-5), the design and components of a rehabilitation intervention and its potential use for pain management in PWH has not previously been evaluated. Furthermore, it remains that the potential feasibility of a telerehabilitation approach for delivering an exercise-based intervention for PWH with chronic pain remains unknown. A feasibility study design was chosen here so as to evaluate if the REMAP-Haemophilia study was acceptable and safe for people with severe haemophilia living with chronic pain, and if it was feasible to be delivered by specialist physiotherapists in haemophilia centres. There was, therefore, no requirement for a control arm for the study. Whilst the feasibility study did not set out to evaluate efficacy as a primary outcome, a preliminary, descriptive evaluation of efficacy was included as a secondary outcome.

6.2 Study aims and objectives

The overall aim of this study was to evaluate the feasibility of a physiotherapy-led, low impact, moderate intensity telerehabilitation intervention in PWH who have chronic joint pain related to haemarthropathy. Evaluation of objectives were carried out using quantitative and qualitative approaches.

The primary objectives identified for the study were:

1. To determine the safety of an exercise based telerehabilitation intervention for PWH
2. To test the feasibility and acceptability of the delivery and content of the telerehabilitation intervention
3. To determine the willingness of clinicians to recruit to the study
4. To determine the acceptability of the overall intervention – recruitment rate, adherence to the intervention, attrition, and study completion rate
5. To identify if the proposed outcome measures are acceptable and suitable

The secondary objectives identified for the study were:

1. To collect preliminary efficacy data (before and after) of intended patient reported outcome measures (PROM's)
2. Establish the usefulness of the chosen PROM's and parameters for use in future studies

The criteria to determine success in the feasibility study were:

1. Five participants per site would be recruited within eight weeks of site becoming open
2. Adherence/ attendance at the sessions would be 75%
3. Less than 20% would report an Adverse Event related to participating in the study
4. Physiotherapists would deliver the intervention according to the protocol (100%)

6.3 Methods

6.3.1 Study design

This is a multi-site, non-randomised, pre-post feasibility study with an explanatory-sequential nested qualitative study. The mixed methods research approach meant that the quantitative and qualitative data were analysed separately according to the philosophical position and methodological approach ascribed to them before being integrated for analysis in keeping with the mixed methods approach chosen (Figure 32).

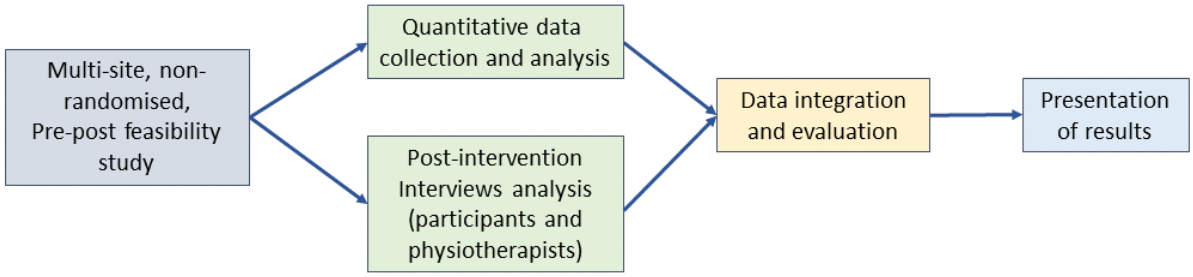


Figure 32: Mixed methods convergent design used in this study

6.3.2 Study setting

This feasibility study took place in two haemophilia comprehensive care centres in England. Such centres have large numbers of PWH registered, and as part of their 'comprehensive care centre' status employ a named, highly specialist physiotherapist who is responsible for the overall provision of expert musculoskeletal care to those registered there. The physiotherapist led the telerehabilitation sessions from the haemophilia centre/physiotherapy department, whilst the participants took part in their own homes.

6.3.3 Study resources

Each site was required to be able to deliver telemedicine (due in part to the ongoing Covid-19 pandemic) using whatever digital platform was agreed locally. An iPad and iPad stand were provided to each site to use if their current webcam/computer set-up at work was inappropriate for delivery of the intervention (e.g. being in a shared office or a room with limited space). Participants needed to have access to a

webcam/internet at home to be able to access the virtual platform. Exercise bands with varying resistances were issued to each centre to be issued to participants as required.

6.3.4 Participants

Potential participants were identified by the centre physiotherapist in advance of attendance at their routine haemophilia clinic reviews. Their eligibility was screened from their medical notes and MDT discussions, and after being approached in clinic about their interest in participating in the study they were then issued with a participant information sheet (PIS)(Appendix P). The PWH member of the research management team (CS) helped develop the content and design of the PIS. Potential participants were contacted by the centre physiotherapist one week after clinic attendance to check if they wished to participate.

6.3.5 Inclusion and exclusion criteria

Inclusion criteria were:

- People with severe haemophilia A or B (with or without an inhibitor)
- Aged 18 years and over
- Self-reported symptoms of chronic pain associated with haemophilic arthropathy in any joint
- Willing and able to give informed consent for participation in this study
- Able to follow instructions
- Have a good command of written and spoken English
- Registered at a UK located haemophilia comprehensive care centre with a named physiotherapist
- Have access to a laptop/tablet with webcam at home and sufficient internet connection

Exclusion criteria were:

- People with mild or moderate haemophilia A or B
- Any other inherited bleeding disorder
- A diagnosis of chronic pain that is not associated with HA
- Severe and/or unstable cardiovascular disease
- Severe and/or unstable pulmonary disease

- Uncontrolled diabetes mellitus

6.3.6 Recruitment and consent

Potential participants were permitted as much time as they needed to decide on whether or not to take part. If they had still not decided at the follow up telephone call one week after clinic, a further follow up phone call was organised at a mutually agreed time. The physiotherapist at each site made explicitly clear to all potential participants that any questions or queries about the study were very welcome.

Although there was only one consent form, it had two distinct parts. Part one was for those who, on declining to participate in the intervention, where then asked if they would want to agree to participate in a short interview to explore their reasons for decline. The second part of the form was for those who agreed to participate in the study itself and included agreement to be interviewed on completion of the study.

The consent forms were available as both hard copies as well a digital version that permitted digital signatures for response (Appendix Q). This meant that multiple non-essential visits at the haemophilia centre were not required due to the ongoing Covid-19 pandemic. This was also advantageous as many PWH registered at specialist haemophilia centres do not live near those centres and so reduced the burden of having to attend the centre in person to complete the consent form.

The study procedures are summarised below in Figure 33.

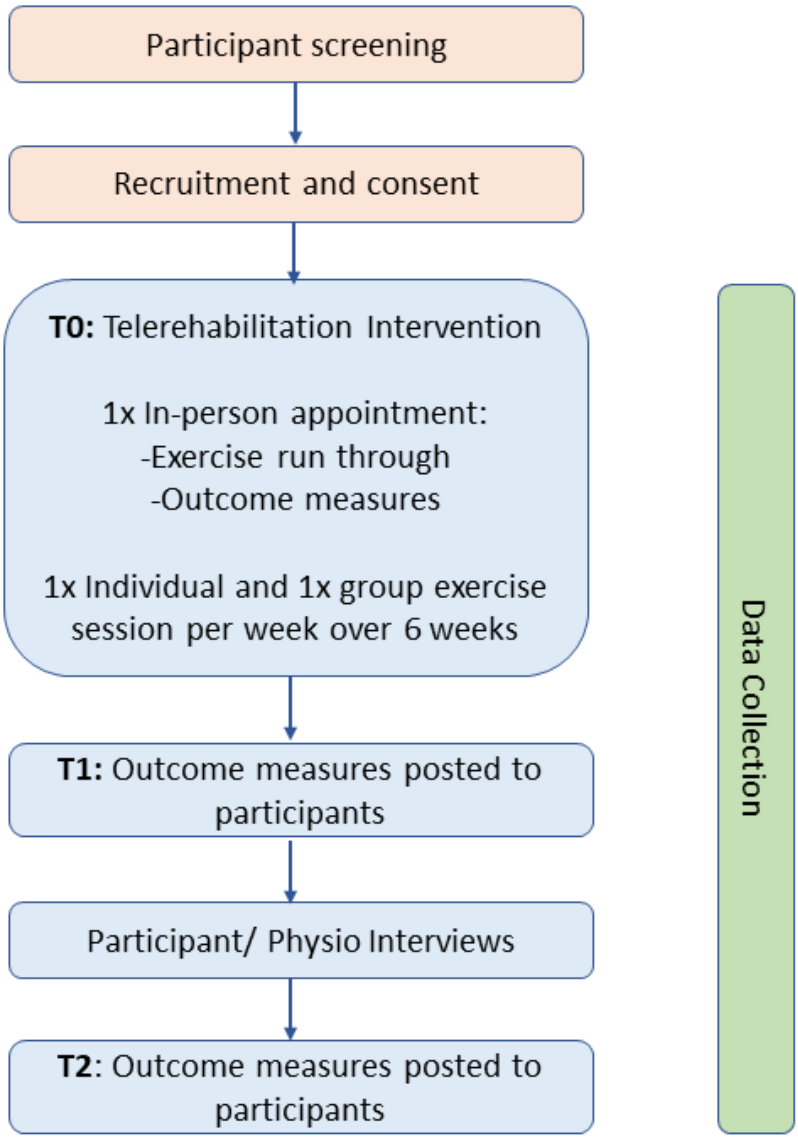


Figure 33: Flowchart of study procedures

6.3.7 Data collection

6.3.7.1 Participant characteristics

Baseline demographic data was collected from review of medical notes and recorded in an individual Case report form (CRF) (Appendix R). This included:

- Demographic information – date of birth, gender, ethnicity, height, and weight
- Social History – accommodation, occupation, social support, family
- General medical history
- Haemophilia specific medical history – haemophilia diagnosis (type and severity), inhibitor status, current haemophilia treatment regime (product name, dose, frequency), type of prophylaxis, bleed dose, number of bleeds reported in the past 12 months, presence of target joints as defined by the International Society for Thrombosis and Haemostasis
- Surgical history – general and orthopaedic
- Analgesic use – name, dose, frequency
- Other medication – name, dose, frequency
- General physical status – mobility, joints affected by haemophilic arthropathy, use of splints or supports

6.3.8 Outcome measures

6.3.8.1 Feasibility outcomes

Thresholds for feasibility outcome were identified a-priori and are detailed in Table 15.

Table 15: Thresholds for evaluation of study feasibility

Outcome	Domain	Indicator of success
Recruitment rate	Number of participants recruited over 8 weeks	5 per site
Consent rate	Number of eligible people approached against those who consented	>75%
Adherence	Attendance rate for all sessions in the study	> 75%
PROM completion	Completeness of PROMs at each time point	> 75%
Fidelity to the protocol delivery	Delivery of protocol assessed against: - delivery of exercises as described - delivery of sessions virtually as described	100%

6.3.8.2 Recruitment

This was defined as the number of people who were recruited at each site compared against the expected and feasible recruitment rate. It was expected that each site could recruit five participants over an 8-week period. The consent rate was calculated with the number of eligible people approached to participate against those who consented. Willingness and ability of the physiotherapists at each site to recruit was evaluated in the post-intervention interview.

6.3.8.3 Safety

This was evaluated by the number of reported adverse events/ serious adverse events recorded at each site. Perception of safety whilst taking part in the study was also evaluated in the participant post-intervention interviews.

6.3.8.4 Adherence

This was evaluated using the attendance figures for each session recorded by the physiotherapists as well as the entries in the physiotherapist diary relating to the delivery of the intervention on a weekly basis. The participant diaries were also used to evaluate adherence to the sessions as well as anything else that was added in addition to the described sessions.

6.3.8.5 Completion and attrition

The numbers completing the intervention were collected from the physiotherapist diaries. Missing data points (diaries, outcome measures) were recorded for each site.

6.3.8.6 Acceptability

Acceptability of the content and the delivery of the intervention, as well as the outcome measures used was evaluated from the post intervention interviews (participants and physiotherapists).

6.3.8.7 Fidelity

Fidelity was defined as competent delivery of the intervention as it was described in the protocol. It was evaluated from the physiotherapist diaries and the post intervention interviews, and focussed on the method of delivery as well as the content delivery of the exercises as described in the protocol.

6.3.8.8 Resources and study management

An understanding of the organisational, delivery and administrative aspects of the intervention was evaluated from the post intervention interviews with the physiotherapists and the entries in the physiotherapist's diaries.

6.3.9 The REMAP-Haemophilia intervention

The overall protocol included behaviour change techniques that were identified and mapped on to the intervention design – this process and the BCTs identified and included has been described in detail in chapter 5.

This was a 12 session (6 week), low impact, moderate intensity exercise-based intervention delivered virtually using the Microsoft (MS) Teams digital platform. Each week there was one individual exercise session and one group exercise session. In addition, three 'knowledge sharing and discussion' sessions were delivered at the start of the group exercise session at week one, three and five of the intervention.

All participating physiotherapists received training in advance of the study commencement. It included background information about the development of the study, training in the delivery of protocol, study delivery/ management requirements and on the inclusion of BCT's and their role in delivering these as a specific aspect. All training was done virtually on MS Teams.

6.3.9.1 Pre-study procedures

Once signed consent had been obtained, participants were invited to an in-person appointment with their physiotherapist. At these sessions they received information, demonstrations, and the chance to practice the exercises included in the intervention and were also required to complete the study outcome measures. The aim was to individualise each exercise and to agree on a starting point for each exercise that best reflected their own abilities. Participants were advised to try and aim to exercise at a moderate level of exertion. Each was given a copy of the Rated Perceived Exertion (RPE) scale to use at home as a visual reminder and to work at between 4-6 on this scale (Appendix V).

The physiotherapist arranged a technical 'dry run' virtual session in advance of the real intervention. This was so the participant and physiotherapist could experience using the MS Teams platform, as well as establishing the best position in the participants own home for the webcam to be positioned for maximum visualisation for both parties.

6.3.9.2 Exercises

The complete exercise set was informed by the outputs from the developmental phases detailed in the previous chapters. It was designed to include the upper and lower limbs, as well as comfortably challenge cardiovascular effort. Table 16 details the exercises included as well as the levels of difficulty. The initial face to face assessment provided each participant with their own starting point on the difficulty level of each exercise.

A short 2 minute warm-up before each session included gentle movements of body and limbs, in keeping with the type of exercises described in the overall exercise plan. The lower impact level was incorporated to limit mechanical stress on those with haemophilic arthropathy of the ankle.

The physiotherapist led every session, gave the instructions for each activity, monitored effort and participation ability, provided feedback and encouragement, and kept time. Each exercise was repeated three times per set and timed at 30 secs of moderate exertion (as per the RPE score card with each participant), 30 seconds rest, and a 2-minute break in between each set. Exercises included resistance (body weight or additional) and cardiovascular with an additional exercise being added to the overall session plan every two weeks. A short 1-2 minute cool down, similar in content to the warm-up, concluded each session.

The total time needed per exercise session was designed so as not to exceed a total session time of 40 mins by the end of week six. This approach to the components and design of the session was directly informed by the stakeholders involved in the theory development.

Table 16: Exercise description and level of difficulty for the REMAP-Haemophilia study

	Level	Exercise	Sets		
			1	2	3
	↑	Standing squat – deep or with weight			
1	---	Standing squat (chair support if needed)			
	↓	Standing mini squat with hands on chair for support			
	↑	Changing step stand and punch – Right then left then right			
2	---	Step Stand punch forward – static			
	↓	Seated alternate arm punch forward			
	↑	Seated bilateral leg lifts (knee bent- straighten leg- knee bent)			
3	---	Seated bilateral leg lifts (knee bent)			
	↓	Seated alternate legs lifts			
	↑	Shoulder circles holding small weights			
4	---	Shoulder circles			
	↓	Repeated shoulder abductions			
	↑	Box stepping at speed			
5	---	Walking/Stepping on spot with high knees			
	↓	Walking on spot			
	↑	Floor based push ups			
6	---	Push ups from bench/table			
	↓	Wall push ups +/- using a ball to accommodate elbow arthropathy			
WEEKS 3/4 ADDITION					
	↑	Alternate leg stationary lunge (+/- holding theraband)			
7	---	Stationary lunge			
	↓	Mini stationary lunge (+/- chair support)			
WEEKS 5/6 ADDITION					
8	↑	Seated/standing biceps curl to shoulder flexion with theraband			
	---	Seated/standing biceps curl with theraband			
	↓	Seated/standing biceps curl no resistance			

6.3.9.3 Knowledge sharing and discussion group session

The content of the three knowledge sharing and discussion sessions was informed by the findings of the qualitative inquiry (chapter 4) and the theory development theory of change process (chapter 5). These sessions were scheduled to occur in the group sessions one, three, and five, and then followed by the exercise activity. Delivered over MS Teams, the sessions focussed on 1). Why we experience pain and what is means, 2). Physical activity (benefits and struggles) and 3). Pacing and finding you own level. Each session was led by the physiotherapist, who presented a short PowerPoint style presentation which included points for a group discussion. The aim was to encourage a forum for participants to discuss shared experiences of pain and activity, and any actions or activities they had found to be helpful for them. The PowerPoint slides used in each session can be found in Appendix W.

6.3.10 Outcome measures

The participant outcome measures were collected at three time points – pre intervention (T0), on intervention completion (T1) and at 12 weeks post intervention completion (T2). The pre-intervention measures were collected in person at the initial face to face session, with the remaining two time point outcome measures being posted to participants with a prepaid, addressed envelope. Copies of the outcome measures can be found in Appendix S.

6.3.11 Measures of pain

6.3.11.1 Brief pain inventory (BPI-SF)

This nine-item self-administered questionnaire takes 5 minutes to complete and is used to evaluate the severity of a person's pain and the impact of this pain on their daily functioning. It is widely used in a range of non-malignant pain conditions (349). Using a 0-10 scale, the patient rates their pain at its *worst*, *least* and *average* in the past 24 hours as well as *right now*. Using the same 0-10 scale they are then asked to rate how much pain has interfered with activities, mood, sleep, and life enjoyment in the past 24 hours. It is recommended that all four questions relating to pain severity (question 3-6) are used and reported as separate scores. The seven items relating to pain interference (question 9) are scored as a mean, as long as more than 50% of the items are completed (349). Whilst it has been shown to have good test-retest

reliability and high construct validity when used in PWH (350, 351), its responsiveness is as yet unknown.

6.3.11.2 Pain Self-Efficacy questionnaire (PSEQ)

Developed in 2007, the pain self-efficacy questionnaire is a 10-item questionnaire that assesses the confidence of people (with any type of chronic pain) in activity despite pain. Each item's response is on a 7-point scale and is scored 0-6. It is an additive score between 0-60, whereby an higher score indicates higher self-efficacy beliefs (352). Although its use in PWH has not been reported, a recent systematic review has reported the PSEQ to have excellent validity, reliability and responsiveness in people with musculoskeletal disorders (353). The same review also reported the minimal clinically important change (MCID) to be in the range of 5.5-8.5.

6.3.12 Measures of Quality of Life

6.3.12.1 EQ5D-5L

The 5-level EQ5D-5L was introduced by the EuroQol group in 2007. It is a 5-item questionnaire evaluating generic health-related quality of life and is usually reported as an overall utility score, alongside an overall health report on the visual analogue scale (VAS) (354). The five dimensions are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. They are scored on 5 levels of no problems (1), slight problems (2), moderate problems (3), severe problems (4) and extreme problems (5). These scores can then be converted into an overall utility index score, with a maximum score of 1 representing the best health state. The VAS is a self-rated health state on a scale ranging from 'The best health you can imagine' at 100, to 'The worst health you can imagine' at zero. The EQ5D-5L has been shown to have satisfactory construct validity in PWH (350, 355). A minimally important difference (MID) in the index score has been suggested between a range of 0.037 and 0.069 (356), although such estimates are based on large population models and may not translate well to smaller studies with unique disease groups.

6.3.12.2 MSK Health Questionnaire (MSK-HQ)

This is a short 14-item questionnaire that allows people with musculoskeletal conditions (such as arthritis related pain) to report their symptoms and quality of life in a standardised way. It has been designed and validated for use across different musculoskeletal pathways in different healthcare settings (357). Questions relate to

pain/stiffness in the day and night, problems with activities of daily living, sleep disturbance, emotional wellbeing, and confidence in managing symptoms. It is scored additively on a range of 0-56, whereby a higher number indicates better musculoskeletal status. It has been shown to be responsive across a range of musculoskeletal conditions with a clinically relevant MCID identified as a score of 6 and over (358).

6.3.13 Measures of Function

6.3.13.1 Haemophilia Activities List (HAL) Questionnaire

The HAL is a questionnaire that measures the impact of haemophilia on self-perceived functional abilities in adults with haemophilia. It has 42 multiple choice questions across seven domains. They evaluate lying/sitting/kneeling/standing (8 questions), functions of the legs (9 questions), functions of the arms (4 questions), use of transportation (3 questions), self-care (5 questions), household tasks (6 questions) and leisure activities and sports (7 questions). Each question is rated on a difficulty of impossible, always, mostly, sometimes, rarely, and never. The total score between 0-100 is calculated from across all domains, whereby a higher score indicates less perceived functional impairment. It has been shown to have good internal consistency and convergent validity in PWH (71). It has yet to be investigated for a clinically relevant MCID, although a smallest detectable change (SDC) score of more than 10.2 points has been reported (359).

6.3.13.2 Patient specific functional Score (PSFS)

This is a self-reported measure that aims to assess functional change in patients presenting with predominantly musculoskeletal disorders. Prior to commencing an intervention, it asks people to identify up to five important activities that they are unable to perform or are having difficulty with as a result of their problem. They then rate the current level of difficulty associated with each activity on an 11-point scale (0-10). At the end of the intervention, they then rate the same activity to identify if there has been any change. Whilst it has been found to be reliable and responsive in people with knee dysfunction and spinal dysfunctions (360), it has never been tested in PWH. The minimum detectable change score per activity is 3 points or 2 points when taken as an average across all scores (361).

6.3.14 Measuring overall change

6.3.14.1 Patient global impression of change (PGIC)

This is a single question completed at the end of the intervention that measures a change in an individual's clinical status. They are asked to rate their change in their own clinical status on a 7-point scale, from very much improved to very much worse. Although the PGIC has been proposed to be a useful anchor by which to determine a MCID from other outcomes used alongside it (362), it was used here as a person centred evaluation of participation in the study.

6.3.15 Diaries

Participants were issued with a one-page, two-question diary to be completed each week whilst in the study (Appendix T). One question asked them to reflect on their experience of the exercise that week and the second asked if they had noticed anything different about themselves as a result of taking part (such as more pain, change to mobility etc). On finishing the exercise intervention, participants were asked to send their completed diaries back in the same envelope as the outcome measures.

The physiotherapists delivering the study were also asked to complete a weekly diary (Appendix U). The aim was to record their thoughts and reflections on practicalities of delivery of the study, feedback, or comments they had received from participants, technical issues and any changes they made to how they delivered the study.

6.3.16 Interviews

6.3.16.1 PWH participants

The nested qualitative study is in keeping with the explanatory-sequential mixed methods design. Whilst consent for this interview was included in the initial consent form (including decliners to the study), all those completing the exercise session component of the study were contacted by email or telephone to confirm if they still wished to be interviewed, with an interview time then arranged at a time convenient for them.

A topic guide was developed with CS (PWH member of research management group) for the post-intervention interviews (Appendices X and Y). Semi- structured interviews were conducted over Microsoft Teams or on the telephone. Questions were open ended and aimed to gain an insight into each person's experience of taking part in the

exercise intervention, as well as drawing focus to the objectives relating to the feasibility and acceptability of the intervention.

Whilst interviews were conducted on MS Teams, only the audio of the proceedings was recorded. The telephone interviews were also audio recorded and all participants agreed to the recording. The audio files were then transcribed verbatim by a professional transcription service.

6.3.16.2 Physiotherapists

Each participating physiotherapist was interviewed on completion of the intervention. They were offered an interview face to face, or a virtually using MS Teams at a time convenient for them. As with the participant interviews, a topic guide was used to inform the semi structured interviews with a focus on feasibility, acceptability, and fidelity of the delivery of the study as well as general feedback and overall views of having taken part. The interviews were recorded and transcribed verbatim.

6.3.17 Data analysis

Participant demographics and characteristics were tabulated. A CONSORT diagram describes the flow of participants through each stage of the study to include enrolment, participation, follow up, lost to follow up and analysis.

6.3.17.1 Quantitative data analysis

Descriptive statistics were used to assess the feasibility objectives (recruitment rate, consent rate, adherence, safety, outcome measure completion at each time point) using Excel. Due to the low numbers of participants and in keeping with the feasibility design, continuous variables (outcome measures) are summarised using median, interquartile range and range for individual and group changes between time points.

6.3.17.2 Qualitative findings (including the diary entries)

NVivo (Release 1.6.1 version) was used to manage the dataset (transcripts and diaries). It was not used to generate codes or themes, only to facilitate the analytic process undertaken by the researcher. (Appendix Z)

Acceptability of the intervention was evaluated from analysis of the participant and physiotherapy interviews and diaries. Transcripts were checked for accuracy against the recording.

The approach to the qualitative data analysis was considered in three stages. The interview data and the diary entries from the participants and the physiotherapists were first analysed together using reflexive thematic analysis approach. The approach has been described in detail previously in Chapter 4, although an overview of the analysis process is now presented. Reflexive thematic analysis is described by Braun and Clark as a six phase recursive approach comprising 1) familiarisation with the data, 2) coding, 3) generating initial themes, 4) reviewing and developing themes, 5) refining, defining and naming themes and 6) writing up (272, 274). The defining feature of this approach is the initial organic development of codes and later theme development, with the researcher's engagement in the data central to analysis and interpretation. This approach serves to create a meaningful account of the experiences of all who took part in this study.

The second stage to the data analysis was to review again the now completed thematic analysis alongside the initial coding structure. This enabled an analysis of the domains relating to the feasibility and acceptability objectives, helping inform the integration of the qualitative findings with the quantitative data. In keeping with the mixed methods approach, the quantitative and qualitative results were tabulated and presented in a joint display, enabling a deeper analysis of the feasibility, acceptability, and preliminary efficacy objectives of the study.

The third and final stage of the data analysis was to review the coding structure and identify those relating to behaviour change, using the list of behaviour change techniques as a matching guide.

6.3.18 Research ethics

The study was given ethical approval by the East Midland- Nottingham 2 Research Ethics Committee (Rec Reference number: 21/EMI/0161). The study was sponsored by the Royal Free London NHS Foundation Trust (Reference number: 141604). (Appendices N and O)

The study was registered in the ISRCTN registry: identification number- 17454597.

6.4 Summary of chapter

This chapter has outlined the rationale for a feasibility design. Descriptions of the processes in conducting the mixed methods analysis and evaluation of the feasibility, acceptability and preliminary efficacy of the intervention have been provided. The following chapter presents results of the REMAP-Haemophilia feasibility study.

Chapter 7 - Feasibility study results

This chapter presents the results of the REMAP-Haemophilia feasibility study. Whilst there are no agreed guidelines for the reporting of studies using a mixed methods research approach, O'Cathain and colleagues propose the Good Reporting of A Mixed Methods Study (GRAMMS) recommendations as a way of standardising the approach (363). In keeping with these guidelines the chapter describes the sequence of the methods, the data collection and analysis approaches used for both quantitative and qualitative data, how the data is integrated and the limitations of one method against the other, and the insights gained from integrating the data. The results described in this chapter are therefore reported in a way that fulfil this approach.

The results will provide a detailed evaluation of the feasibility, acceptability and efficacy of the REMAP-Haemophilia study and will be presented in three parts. Part 1 will describe the quantitative results, Part 2 will present the findings of the nested qualitative study, and Part 3 will be an integrated presentation of the quantitative and qualitative results.

7.1 Study recruitment

Two large regional haemophilia centres participated in this feasibility study. Over a period of eight weeks 24 people were screened for eligibility from upcoming clinic lists, of whom 13 were approached and invited to participate, 3 declined citing lack of interest (n=1) and lack of time (n=2). Ten people provided written consent to participate. The flow chart below details the recruitment and retention for the study (Figure 34).

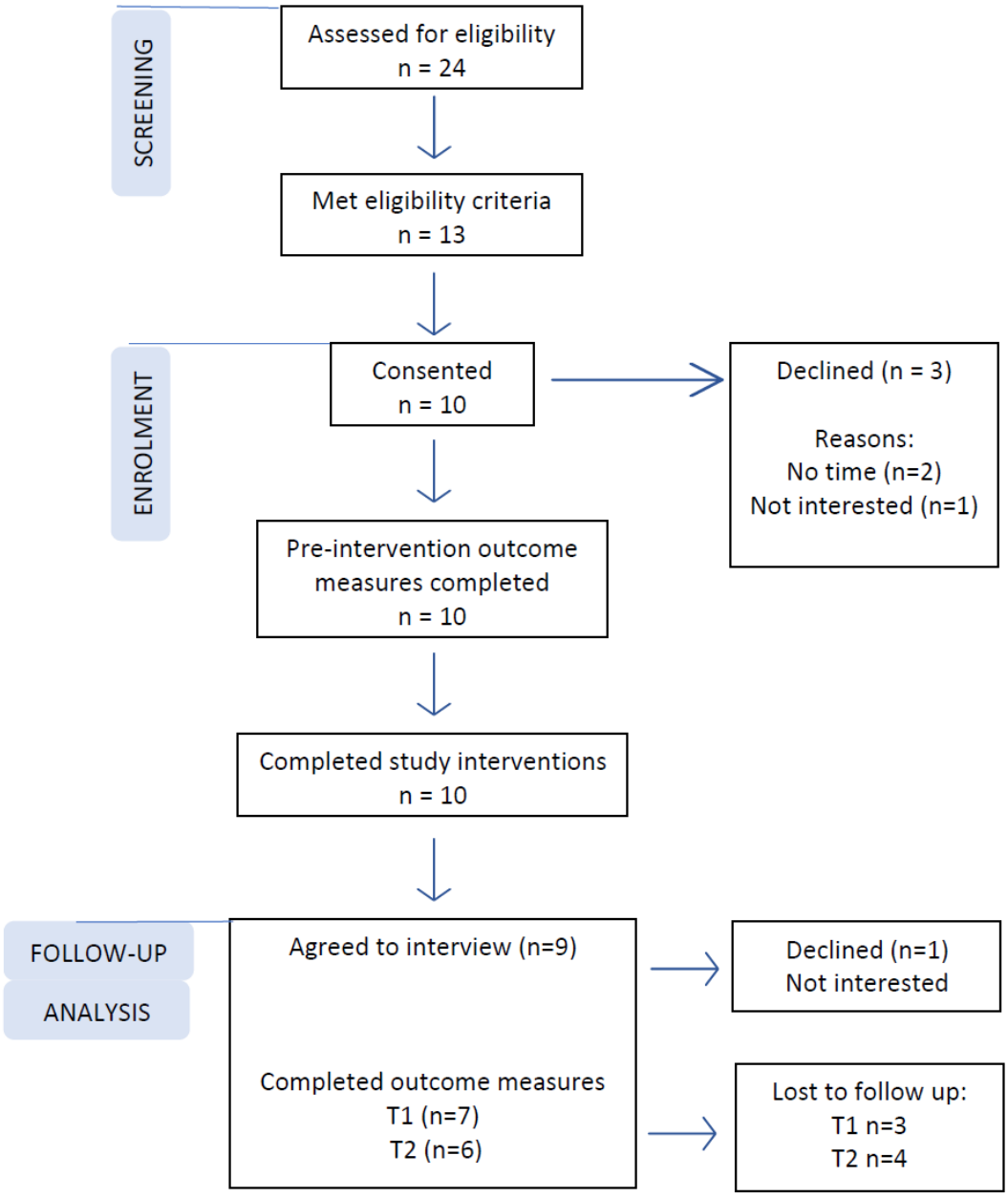


Figure 34: Recruitment and retention of participants in REMAP-Haemophilia study

7.2 Participant characteristics

An overview of participant details is presented in Table 17. Ten male participants aged between 39 and 67 (median age 57) were recruited to the study. Nine had a diagnosis of severe haemophilia A, one had severe haemophilia B. Nine were on regular prophylaxis (ranging from once a week to once a fortnight) and one was using a prophylaxis regime targeted to activity. None reported the presence of any target joints as defined by the International Society for Thrombosis and Haemostasis (i.e. 3 or more haemarthroses into the same joint in past 6 months)(19). Six participants described themselves as independently mobile, three used mobility aids intermittently if in pain (cane or crutches) and one used a mobility scooter for longer distances outside. Eight participants had other health-related comorbidities, the most reported being previous Hepatitis C (HCV) now cleared secondary to eradication therapy (n=8), HIV (n=4) and hypertension (n=3).

All participants had chronic pain as defined by the International Association for the Study of Pain (94) that was present for more than 3 months. Pain medication varied. Medications used daily included COX-II inhibitors (Celecoxib, Eterocoxib) (n=3) and opioid based medications (Tramadol, dihydrocodeine, Oramorph) (n=3) and neuropathic pain medication (Pregabalin) (n=1). Pain medications taken on an as and when basis included acetaminophen (n=5) and opioid based medication (n=3). Of the nine people for whom a Haemophilia joint health score (HJHS) was available, 8 people had 4 or more joints affected by haemophilic arthropathy, with 4 people having six affected joints (bilateral elbow, knee and ankle).

Walking (n=4) and a basic home exercise programme (n=4) were the most reported physical activities along with swimming (n=1), cycling (n=1) and golf (n=1).

Table 17: Participant demographics of REMAP-Haemophilia study

Variables	n	Median (IQR)
Gender - Male	10	
Age		57 (21)
BMI		25.95 (2.8)
Diagnosis		
- **SHA**	9	
- **SHB**	1	
Prophylaxis	10	
- **Trial product**	1	
- **Hemlibra**	3	
- **Standard Half Life FVIII**	1	
- **Extended Half Life FVIII**	4	
- **Extended Half Life FIX**	1	
Employment		
- **Full time**	3	
- **Part time**	1	
- **Retired**	4	
- **Unemployed**	2	
Ethnicity		
- **White British**	8	
- **Chinese**	1	
- **White Other**	1	
Joints with Haemarthropathy		
- **3 or less affected joints**	2	
- **4 or more affected joints**	8	
Co-morbidities		
- **HIV**	4	
- **Hypertension**	3	
- **Liver Disease**	1	
- **Osteoporosis**	1	
- **Peripheral Neuropathy**	1	
- **Portal Hypertension**	1	
- **Hypothyroidism**	1	
- **Atrial Septal Defect**	1	
- **Previous HCV (cleared)**	8	
Pain Medications		
- **Acetaminophen**	6	
- **Cox-II inhibitors**	4	
- **Opioids**	6	
- **Other - Pregabalin**	1	
- **Other – Cannabis**	1	
Major Orthopaedic Surgery		
- **Ankle Arthrodesis**	4	
- **Total Knee Arthroplasty**	3	
- **Total Hip Arthroplasty**	4	

7.3 Part 1 – Quantitative results: feasibility and efficacy

7.3.1 Feasibility of intervention

7.3.1.1 Recruitment rate

The target recruitment was 5 per site. One site over-recruited by one participant (n=6) and the other site under recruited by one participant (n=4). Of the 13 identified eligible people approached to participate 10 agreed, representing a consent rate of 77%. These outcomes indicate that both recruitment and consent were a success within the scope of the feasibility threshold. The three decliners did not agree to be interviewed.

7.3.1.2 Adherence and attendance

The study protocol described the delivery of 12 sessions in total. Six of these sessions were a once weekly 1:1 session and six were weekly group sessions, three of which included a knowledge and discussion session held before the exercise session.

There was an overall attendance rate of 68.3% for the study intervention, failing to meet the 75% threshold identified for success. When analysed per session type, attendance rate for the 1:1 session was 84.5% and for the group sessions was 52.1%. There were between-site differences in the attendance rates for the group sessions. Site 01 had 91.7% and Site 02 12.5% attendance for the group exercise sessions.

The reasons given for missing individual 1:1 sessions (n=8) included sickness (n=2), recovery from an intra-articular ankle joint injection (n=1), muscle injury unrelated to the study (n=1), joint pain (n=1) and knee haemarthrosis unrelated to the study (n=1), non-attendances with no reason given (n=2). The reasons stated for non-attendance at the group sessions (n=25) were anxiety (n=6), other commitments (n=3), sickness (n=1), flank pain (n=1) no reason given (n=14).

Table 18: Evaluation of feasibility thresholds for study

Outcome	Domain	Indicator	Result
Recruitment rate	Number of participants recruited over 8 weeks	5 per site	Achieved – partial
Consent rate	Number of eligible people approached against those who consented	>75%	Achieved - 77%
Adherence	Attendance rate for all sessions in the study	> 75%	Partially achieved All sessions = 68.3% F:F only = 84.5% Group session only = 52.1%
PROM completion	Completeness of PROMs at each time point	> 75%	Not achieved Pre-intervention (T0) = 100% Post intervention (T1) = 70% 12 weeks post (T2) = 60%

7.3.1.3 Fidelity of protocol delivery

The number of planned sessions to be delivered in the feasibility study was 72 (total of individual and group sessions). The study delivered 61 sessions (84.7%) resulting in 87 (72.5%) personal contacts. These personal contacts were delivered (as per protocol description) virtually using webcams 80.4% of the time, with the remaining 12 (19.6%) being conducted over the telephone.

7.3.1.4 Safety

The incidence, type and severity of adverse events reported whilst participating in the study are presented in Table 19. One participant reported having a painful hamstring the day after the group session in week one and took an extra dose of factor VIII later that evening as a precaution in case of a bleed. He felt fully recovered by the time of his next 1:1 session (five days later). One participant reported a muscle sprain of his left flank whilst doing an activity at home unrelated to the study. Four episodes of increased joint pain (one knee, two elbow, one shoulder) the day after the session were reported by three participants. All resolved within 24-48 hours and no extra factor concentrate was taken, although one participant reported using an ice pack on his ankle to good effect. A knee joint haemarthrosis was reported by one participant

which he reported was not related to the exercises associated with the study. No serious adverse events were recorded for anyone participating in the study.

Table 19: Incidence, type and severity of adverse events recorded in study

Description of event	Number of people	Incidence	Severity
Muscle pain (hamstring)	1	1	Non serious
Muscle sprain	1	1	Non serious
Increased joint pain	3	4	Non serious
Joint Bleed	1	1	Non serious

7.3.1.5 Completion and attrition

All ten participants completed baseline PROMs (T0), with 7 completing them at the end of the intervention (T1) and 6 completing them at 3 month follow up (T2), failing to meet the feasibility threshold of 75%. Nine participants agreed to be interviewed at the end of study. One person declined to be interviewed due to anxiety. There were no missing data points identified on any of the outcome measures returned at T1. There were 2 missing outcome measures for one participant at T2.

7.3.2 Secondary outcome: Efficacy of intervention

Preliminary efficacy of the intervention was evaluated as a secondary outcome in this feasibility study. Changes between timepoints of included outcome measures were examined across the group and on an individual basis.

7.3.2.1 Between time point group median changes in outcome measures

Group changes in measures of pain, self-efficacy, quality of life and function are presented in Table 20.

Table 20: Median Change in Pain, Function, and quality of life before and after intervention

		Group Median (IQR) at study timepoints			Median Change between timepoints	
Domain	Outcome Measure	T0 (n=10)	T1 (n=7)	T2 (n=6)	T0-T1	T0-T2
Pain	BPI-SF					
	- Worst pain	7 (5)	7 (4)	5 (2)	0	-2
	- Least pain	2 (3)	2 (3)	2 (2)	0	0
	- Average pain	4 (2)	5 (2)	4 (4)	1	0
	- Pain now	3 (4)	3 (4)	3 (4)	0	0
	- Pain interference	5 (5)	3.42 (3.15)	3.28 (3)	-1.58	-1.72
Self-Efficacy	PSEQ	45 (27)	39 (27)	37 (20)	-6	-8
HR-QoL	EQ5D-5L - VAS - Utility Score	 70 (35) 0.649 (0.308)	 75 (40) 0.389 (0.358)	 70 (10) 0.698 (0.07)	 +5 -0.26	 0 + 0.049
	MSK-HQ	30 (14)	39 (14)	35.5 (7)	+9	+5.5
Function	HAL (Sum)	46.9 (33)	52.3 (39.1)	49.65 (19.4)	5.4	2.75
	PSFS	3 (1.66)	3 (1)	3.33 (0.84)	0	0.33

The results presented are for those fully completed outcome measures received pre and post intervention (T0 and T1) and at 12 week follow up (T2) with the group median change and interquartile range.

Pain as assessed using the Brief Pain Inventory showed no change in group median with report of '*worst pain,'* '*least pain'* and '*pain now*'. The '*average pain'* increased by one point whereas '*pain interference*' decreased by 1.58, although this was not considered a meaningful clinical difference. This slightly increased again at T2.

Pain self-efficacy as measured using the Pain self-efficacy questionnaire showed a decrease of 6 points at T1, decreasing to 8 points at T2.

Aspects of quality of life were measured using the EQ5D-5L and MSK-HQ questionnaires. The EQ5D-5L scores were presented as change in VAS, which showed a 5-point increase, and the overall utility score, which showed an overall decrease of 0.26 at T1, but improving again at T2. The MSK-HQ increased by 9 points at T1 and still maintained a 5.5-point increase at T2.

Self-reported function as measured by the HAL questionnaire showed a small increase of 5.4 points from 46.9 to 52.3, returning to baseline score at T2. The PSFS questionnaire showed no change from baseline to post intervention and minimal change at T2.

7.3.3 Between timepoint individual changes in reported outcome measures

Individual changes from T0, T1 and T2 in participant reported outcome measures are presented below. Where an MDIC or SDC value is established for the outcome measure, results are compared against this to evaluate if significant change has occurred.

7.3.3.1 Change in pain – BPI and PSEQ

Table 21 presents the individual changes to scores as measured using the BPI questionnaire.

At T1, an increase in '*worst pain*' was reported by 4 participants, with 2 remaining the same and 1 reporting an improvement. '*Least pain*' was rated as worse by 3 participants, unchanged in 1 and improved in 3 people. Reports on '*average pain*' saw an increase post intervention in 5 participants and was unchanged in 2. '*Pain now*' was reported as having increased by 3 people, unchanged in 2 participants and improved in 2. The overall '*pain interference*' score for 3 participants increased while 4 reported an improvement, of whom only 1 demonstrated an improvement in minimal detectable change, which was sustained at T2.

Table 21: Changes in individual Brief Pain Inventory-Short Form score between timepoints

Participant ID	*Worst pain*			*Least pain*			*Average pain*			*Pain now*			*Pain interference*		
	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2
1	6	8	7	0	2	3	3	5	5	2	3	6	5	5.6	5
2	2	5	4	2	2	1	3	4	2	1	3	1	3.5	2.7	2.1
3	7	7	6	4	5	3	5	5	6	7	7	5	6.5	5.7	4.4
4	7	6	5	4	2	3	7	7	6	5	2	3	7.5	3.4*	5*
5	7	7	5	2	4	1	4	5	2	3	4	3	2.5	2.9	2
6	1	2	0	1	0	0	1	2	0	0	0	0	0	0.3	0
7	5	9	-	6	5	-	5	6	-	5	0	-	10	8.4	-
8	4	-	-	1	-	-	4	-	-	1	-	-	2.5	-	-
9	9	-	-	4	-	-	7	-	-	6	-	-	5.5	-	-
10	8	-	-	4	-	-	7	-	-	7	-	-	7.5	-	-
Group Median (IQR)	7 (5)	7 (4)	5 (2)	2 (3)	2 (3)	2 (2)	4 (2)	5 (2)	4 (4)	3 (4)	3 (4)	3 (4)	5 (5)	3.42 (3.2)	3.28 (3)
Median Change T0-T1	0			0			+1			0			-1.58		
Median Change T0-T2			-2			0			0			0			-1.72
Key	'-' = Missing data						* MCD = 2.34 for pain interference (364)								

Pain self-efficacy as measured by the PSEQ was unchanged in 1 participant and was reported to be worse in 3 people. Four participants reported improvements in pain self-efficacy, 2 of whom had a significant change, which was maintained at T2. (Table 22)

Table 22: Changes in individual PSEQ scores between timepoints

Participant ID	PSEQ T0	PSEQ T1	PSEQ T2
1	47	15	27
2	45	40	39
3	21	39 *	37 *
4	18	33 *	32 *
5	48	53	-
6	60	60	60
7	36	26	-
8	3	-	-
9	35	-	-
10	17	-	-
Group Median	45	39	37
IQR	27	27	20
Group Median change T0-T1		-6	
Group Median change T0-T2			-8
Key	'-'= Missing Data		
	* MDC = 11.2 (353)		

7.3.3.2 Health related QoL – EQ5D-5L and MSK-HQ

The individual changes in the EQ5D-5L and MSK-HQ questionnaires are presented in Tables 23 and 24. The EQ5D-5L is reported as change in the utility score and changes in the self-reported VAS score. From T0 to T1, 4 participants reported a decrease in the VAS and 1 remained unchanged. The remaining 2 participants reported an improvement in their VAS. Of the 2 participants who reported a small increase in the VAS at T2, only one of these was a sustained increase from T0. With the utility score at T0 to T1, three participant scores worsened and 1 remained unchanged. The scores of the remaining 3 people improved. Two participants had improvements in both their VAS and utility score overall at T1, and only one at T2.

Table 23: Changes in individual EQ5D-5L scores between timepoints

Participant ID	**VAS**			**Utility Score**		
	T0	T1	T2	T0	T1	T2
1	65	40	40	0.777	0.375	0.586
2	80	75	65	0.649	0.649	0.675
3	55	55	65	0.697	0.389	0.697
4	70	80	75	0.469	0.733	0.699
5	80	75	80	0.697	0.71	0.745
6	75	90	75	0.879	0.937	0.922
7	55	35	-	0.393	0.307	-
8	70	-	-	0.47	-	-
9	65	-	-	0.452	-	-
10	25	-	-	0.171	-	-
Group Median (IQR)	70 (35)	75 (40)	70 (10)	0.649 (0.308)	0.389 (0.358)	0.698 (0.07)
Group Median change T0-T1		+5			-0.26	
Group Median change T0-T2			0			+0.049
	'-' = Missing data					

Two participants reported a decrease in the overall MSK-HQ scores at T1. The remaining 5 reported improvement in the MSK-HQ score, with one participant demonstrating a clinically important improvement based on MCID at T1 but not at T2. This same participant also showed improvement in both domains of the EQ5D-5L questionnaire at T1. One participant had a clinically important increase in score at T2 but not at T1.

Table 24: Changes in individual MSK-HQ scores between timepoints

Participant ID	MSK-HQ T0	MSK-HQ T1	MSK-HQ T2
1	30	26	30
2	42	39	37
3	28	33	* 34
4	28	* 40	32
5	36	39	39
6	53	56	54
7	24	21	-
8	31	-	-
9	24	-	-
10	17	-	-
Group Median	30	39	35.5
IQR	14	14	7
Group Median change T0-T1		+9	
Group Median change T0-T2			+ 5.5
	'-' = Missing Data		
	* MCID = 6 (365)		

7.3.3.3 Function –Patient Specific Functional Score (PSFS) and Haemophilia Activities List (HAL)

Table 25 presents the individual changes in the PSFS questionnaire. Two participants demonstrated no change in their PSFS scores at T1 and another two showed a small deterioration in the score. Three participants demonstrated an improvement in their PSFS score, with 1 achieving an increase equivalent to a small change in MID, which was sustained at T2.

Table 25: Changes in individual Patient Specific Functional Score (PSFS) questionnaire score between timepoints

Participant ID	PSFS T0	PSFS T1	PSFS T2
1	5	6	3
2	3	3	3
3	3.33	3	3.67
4	1.6	3 *	4 *
5	2.8	2	-
6	1.67	2	3.33 *
7	3	3	-
8	0	-	-
9	6	-	-
10	3.5	-	-
Group Median (IQR)	3 (1.66)	3 (1)	3.33 (0.835)
Group Median change (T0-T1)		0	
Group Median change (T0-T2)			0.33
Key	'-' = missing data		
	* Minimally Important Difference = 1.3 (small), 2.3 (medium), 2.7 (large) change (366)		

The results for changes in the HAL questionnaire are presented in Table 26. In the HAL questionnaire, 5 participants had an improvement in their overall post intervention score at T1, although the size of the differences varied and only one participant achieved an improvement associated with the smallest detectable change. The remaining 2 participants showed small decrease in the HAL sum score. Four participants had a decrease in HAL scores at T2 to almost baseline scores.

Table 26: Changes in individual Haemophilia Activities List (HAL) sum scores between timepoints

Participant ID	HAL SUM score T0	HAL SUM score T1	HAL SUM score T2
1	66.1	78.9	51.9
2	59.5	52.3	59.4
3	33.9	37.6	40
4	46.9	55.6	47.4
5	37.1	41.9	37.1
6	70.5	76.7	71.4
7	23.9	22.2	-
8	50	-	-
9	57.9	-	-
10	32.8	-	-
Group Median (IQR)	46.9 (33)	52.3 (39.1)	49.7 (19.4)
Group Median change (T0-T1)		5.4	
Group Median change (T0-T2)			2.75
Key	'-' = Missing data		
	* Smallest detectable change (SDC) = 10.2 (359)		

7.3.3.4 Subjective view of change – Patient global impression of change (PGIC)

Participants completed the single question global impression of change at the end of the intervention (T1). One participant reported no change. Another participant rated the current state as being much worse, but the participant diary showed this was due to the presence of low back and leg pain unrelated to his participation in this study. Three participants reported minimal improvement and 2 participants rated being much improved.

7.4 Part 2 – Findings of nested qualitative study

Nine study participants agreed to be interviewed on completion of the intervention, as did both physiotherapists. Anonymised demographic information of the participants is presented in Table 27, and for the physiotherapists in Table 28.

Table 27: Demographic data (anonymised) for interview participants

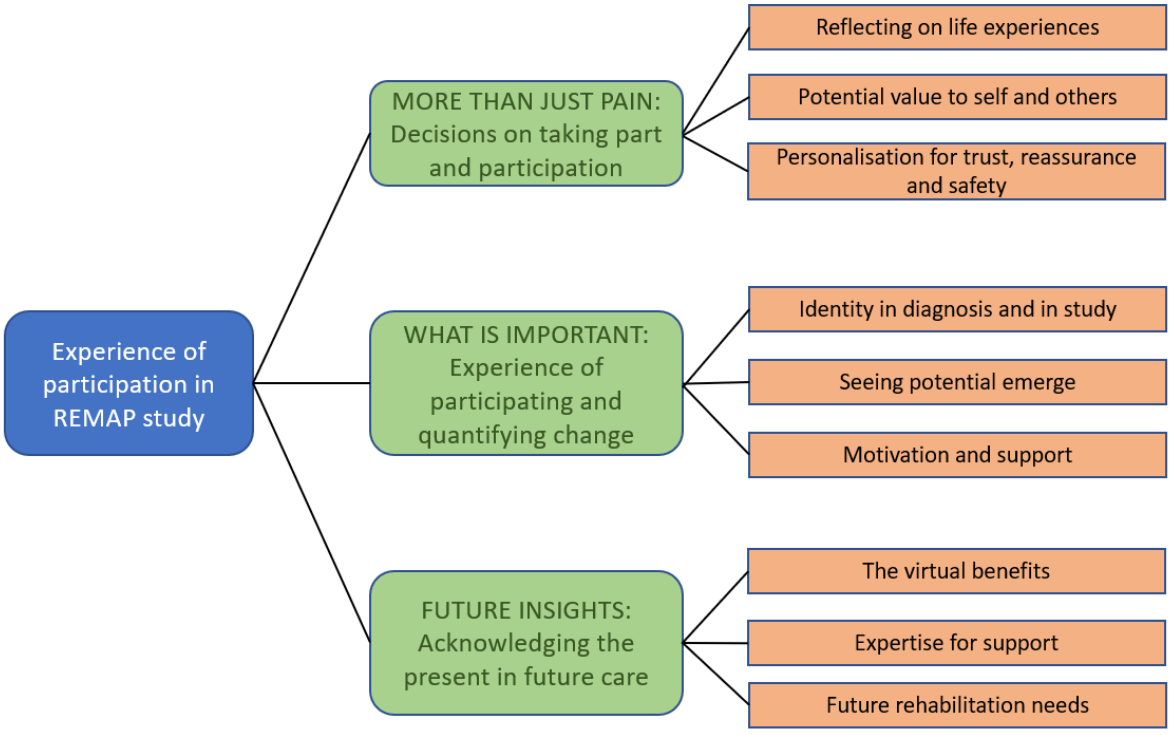
Participants with haemophilia			
Name	Age	Diagnosis	Number of joints with arthropathy
Liam	51	SHA	6
Jack	60	SHA	3
Luke	54	SHA	6
John	61	SHB	3
Adam	63	SHA	6
Mark	67	SHA	6
Carl	42	SHA	2
Hugh	41	SHA	3
Bill	39	SHA	4

Table 28: Demographics data (anonymised) for physiotherapists

Physiotherapists		
Name	Gender	Experience in haemophilia
Dan	M	3 years
Liz	F	15 years

Three themes were conceptualised from the data: Theme 1. More than just pain: decisions on taking part and participation; Theme 2- What is important: Experience of participating and quantifying change; Theme 3- Future Insights: Acknowledging the present in future care. The themes and subthemes are shown in Figure 35.

Figure 35: Thematic map: The experience of participating in the REMAP-Haemophilia study



7.4.1 Theme 1: More than just pain- Decisions on taking part and participation

7.4.1.1 Subtheme: Reflecting on life experiences

Whilst the experience of chronic pain associated with arthritis is one experienced by many, the added complexities of a life lived with severe haemophilia provide a complex layer of life experience from which to base decisions on. As identified in the previous qualitative study (Chapter 4), pain is viewed by many as a normal fact of life and similarly here.

> *"…ankles… They're the ones that I put up with for years and years… it's just become normal to me now and I just … I don't take any painkillers or anything, I just put up with it and just carry on." (Jack, SHA)*

Whilst the acceptance of pain is there, for some the continued evolution of more effective modes of treatment for bleeding has helped them discriminate between pain from arthritis and pain from bleeding.

> *"I've got a number of aches and pains, that is elbows and ankles primarily. Restricted walking, which is really restricted by the ankles. And it's not necessarily the day that you do it – it's often the day after that you pay for it. And that is better with Hemlibra." (Adam, SHA)*

Improvement in this perceived relationship between pain and bleeding has been lifechanging for other putting them in a position whereby they feel physically safe and able to do more.

> *"I started Hemlibra last year… That changed my life – our life, basically – because before Hemlibra I was bleeding pretty much continuously into the joints and we weren't really twigging it. So, now, the Hemlibra's kind of meant that… now I'm actually in a place where I've got more movement, and I never had." (Bill, SHA)*

The ability to discern arthritic pain from bleeding does not get any easier. The ongoing awareness of the possibility of bleeding plays heavy on day-to-day decision making around activity choices;

> *"When you get to my age, you sometimes have pains in the joint which you're not quite sure whether it's just chronic arthritis or whether it's a bleed... It's quite subtle but there is, I think undoubtedly, a difference. When I*

wake up sometimes and my arm feels a bit stiff I think, "Is that a bleed starting or is that actually… is that something else?" (Mark, SHA)

As the underlying anxiety around pain and bleeding was felt to be influential on motivation to exercise, so to were things like the weather's effect on joint pain as well as conflict between knowing they needed to be more active but not getting around to doing so. Past negative experiences of the challenges around hospitalisation also influence the ability to find motivation to exercise.

" I've always been a bit lazy when it comes to doing that sort of… I think from an early age with haemophilia you spend such a long time in hospital that you… there's a bit of an association with… you know, it feels like work and a chore, and I think when you've been pulled around since a very early age that you never kind of... I'm in my 40s now and I still have that reluctancy to do that sort of thing." (Carl, SHA)

The belief that being part of this study would help motivate participants was prevalent throughout responses. There was also the notion that even with the presence of chronic arthritic changes the fact that you '*have to push past the pain and keep going … to get over that early morning hump'* (Jack, SHA) was needed. There was hope too, that even with all the previous negative experiences, it still may well be worth trying to see if change could happen.

"it's finding that belief that the exercises you've been given when you've lived in lots of pain for a long time … that you do get to a place of… "Well, I'll do what you say but this is not going to make any bloody difference." So, I think because it was a study it was very much a case of, "Ok, I'll try anything." If it's a study, I'll give it a go." (Bill, SHA)

7.4.1.2 Subtheme: Potential value to self and others

PWH are a group, who, by virtue of their rare disease and the ongoing development of superior treatments, are very experienced in participating in clinical trials. This experience makes some feel keen to be able to give something back even if there was some doubt about the effects of taking part in a study such as this.

"It sounded like an interesting programme and I thought it would be doing something positive as well, kind of giving something back. I was open-minded. I didn't know if the exercises… I looked at them and I thought, "Well, I'm not sure if they're going to work or not, I'll give it a go. Because I think, well, the centre [has] given me so much over the years, if I can give something back to it then I'd like to do that." (Mark, SHA)

Encroaching pain and the potential for disability was noted as a critical decision point in needing to try and do something.

> *"For many years I've had varying degrees of problems with my right knee – And it got to the stage were earlier this year, it's really bad, and I didn't even go out of the house very much. It's caused me a lot of pain. It was even impeding my ability to get around the house … and that started to kind of affect my mental health as well because I was just thinking, "I'm just housebound, almost." (John, SHB)*

Others acknowledged that whilst pain was an ever-present feature, it was actually their view of themselves as getting older and other co-morbid health issues that piqued their interest in wanting to take part.

> *"I know that the pain I can put up with anyway, so… I mean, all my life… so it's not a big deal anymore, in a way. But my general health is more important. As you get older then you think about more other things than actual pain." (Jack, SHA)*

> *"I'm getting older. I don't want to get diabetes… I've got enough to cope with… I'm a little bit overweight, my BMI is 27. I need to lose three or four kilos still." (Adam, SHA)*

The need to acquire more skills and information about how to better manage themselves and their painful joints also influenced their decision to participate. There was desire to know a different way of doing exercises that may help, as well as creating a structure of what to do and when. Others noted that the time just felt right in being part of a study like this:

> *"I've not had this sort of arthritic problem like I have now… well, it was just a good time to talk about it and it just seemed to be… it seemed to make sense to do that. Because otherwise I only get to the haemophilia centre occasionally to see the physio." (Hugh, SHA)*

There was too a growing realisation that after other medical interventions, a more physically active approach towards pain may provide an answer.

> *"At the moment having these injections done has kind of focused where I think the pain is coming from a little bit more... The tendons, actually the tendons around the joint are still a bit tender, and that makes me think that actually a bit more physio and stuff like that is probably the answer." (Carl, SHA)*

The multiple painful joints experienced by those participating was mentioned throughout. The approach described in the study was seen as worth a go as it would be targeting many joints, not just one.

> *"The majority of us with chronic pain, when it's affecting more than one joint, the biggest problem you have is very much, "Right, you need physio." "Ok, cool." "Right. We're going to do some physio on your leg." "Ok, but what about the rest of me?" And you just end up on this treadmill… and then by the time you've worked on the next joint, the one you were working on originally is now kind of struggling again… So, at least with this it was a little bit more… well, we can hit it from all angles." (Bill, SHA)*

7.4.1.3 Subtheme: Personalisation for trust, safety, and reassurance

There was unanimity in being safe to participate in what was required as part of the study. Whilst in the main this was noted to be related to the type and technique of exercises it was also highlighted as a feeling of safety in inclusion and not being different.

> *"I felt really relaxed. I didn't have to think about… concern about anything. But in a different situation with different people, then you wouldn't be able… you always think about "I'm different to them". And definitely, it makes you just relax a lot more and just get on." (Jack, SHA)*

The established relationship between participants and their physiotherapist was a notable key component of the experience being part of the study. The physiotherapists felt confident on advising the exercises and the virtual delivery due to the fact that they knew the people so well in the day-to-day clinical setting.

> *'… because I know them I know what their joints are like, so I could say, "This one, you haven't got any ankle dorsiflexion, so you're not going to be doing it in this way – you might find it difficult." So, you can kind of picture in your mind the problems that they may have from a mechanics point of view with the different exercises." (Liz, Physiotherapist)*

This trust was reciprocal in that participants were confident in the information they were being told and it would not be harmful.

> *"I'm trusting… I mean, you guys are physios, so I'm trusting that… And it's nice to have that knowledge because if I was to do it myself I would be making it up and hoping that that I'm doing the right exercises, and not knowing if I'm doing my back in five years from now." (Luke, SHA)*

The perceived safety of the completely virtual delivery was also enhanced because of that relationship, which may not have been the case with someone who did not know them as well.

> *"Because I know Liz, it's very much a case of why bother going. I don't necessarily need to – they can explain it to me, knowing the issues. Whereas if I was going to a different physio or someone I didn't know, it would have been a random." (Bill, SHA)*

The perceived importance of needing to be seen to do the exercises on the screen as a mode of enabling a safely delivered intervention was challenged in this study. This was due to episodes of localised Wi-Fi issues as well as the delivery of the exercise sessions over the phone for some people. The physiotherapists were pragmatic about the lack of visuals in some cases relying on the assumption that the activity was being carried out as advised.

> *"There were a couple of people who we did that on the phone rather than having a camera, but that's just… one chap it's just not… that's just not his thing. You just have to take their word for it that they're doing the right thing." (Liz, Physiotherapist)*

Whilst some participants reported lack of visuals on screen due to needing to move away from the camera do some of the exercises (such as against a wall or on the floor), this was not perceived as a negative thing. In fact, for some who used mostly telephone calls to do the intervention, it was the verbal support and instructions alongside the routine that seemed to be the key factor;

> *"I just did it on my phone. I have got a laptop. I think I might have put it on the… yes, I did it on a tablet the first time around, and actually by the end of the study I was just doing it by voice… I mean, I know [the physio] very well but we didn't need to be looking at each other at that point. So, it kind of evolved, natural evolution, from a tablet to a phone to just voice, actually, by the end." (Carl, SHA)*

Engagement in the planned activities from the offset helped establish engagement and a reassurance about what was required. The differing starting points for each exercise depending on individual ability was seen as a wholly positive and helpful approach.

> *"Because we did a quick dry run before we started it, and we went through the list of stuff and then we just had a little go at each one, just to see*

whether it was doable and they were all… they were all doable. At home it felt perfectly safe doing that." (Liam, SHA)

Ongoing advice and feedback to participants was welcomed, particularly in relation to different techniques for each exercise especially if pain or discomfort was limiting activity.

"Dan asked a couple of times, you know… Because my elbow as well is a bit dodgy, so… they said… I think one time it got a little bit… a little bit painful afterwards, but from that point onwards we always just put more weight on my left arm and just… So I felt… yes, I definitely felt safe with doing them – just changed them if need be." (Hugh, SHA)

Whilst this was predominantly done in the individual sessions, some participants also found themselves acquiring hints and tips given to others in the group and trying it out for themselves to good effect.

"And then with the lunge, I picked up on something that Dan had told one of the others, is that to get stable, if you have your feet wider apart… and I tried that and it gave me more stability to kind of… I found that helpful." (John, SHB)

7.4.2 Theme 2 – What is important: experience of participation and quantifying change

7.4.2.1 Subtheme: Identity in diagnosis and in study

As demonstrated in theme 1, the decision to take part in the study was multifactorial as was the experience of being part of the study and the subsequent process of evaluating their experiences of doing so. The physiotherapists were aware of the importance of the study being designed for PWH and how the acknowledgement of this identity was important.

"They hadn't experienced a class like that before. I think they know that classes are available in gyms that you can go to, but I think it's that… I guess identifying as a person with haemophilia and then having a class for people with haemophilia." (Dan, Physiotherapist)

The novelty and relevance of having an exercise intervention that only included others with similar joint disease and physicality was noted positively, helping to facilitate a safe and inclusive experience.

> *"A lot of the time… I always want to do some… not just exercise but doing normal things like going to the gym or even going to the public pool to swim. I mean, even there I think 'Will I fit into that situation? Will people look at me differently?' Your funny joints or whatever. You just can't be relaxed… But without thinking about it, you don't need to think about that [here]. Definitely you feel more enjoyable doing it." (Jack, SHA)*

For those that participated in the virtual group exercise class seeing others with similar '*dodgy elbows*' (Liam, SHA) as them was reassuring, giving insight to others experiencing the same struggles as they lived with. Being part of a group and being in a position to empathise with the pain and arthropathy was reflective and encouraging.

> *"I haven't really mixed with haemophiliac guys since I was a kid – and that was, like, 50 years ago, it was a long time ago. And so, yes… It had a big… I wouldn't say psychological impact, but it was like a big awakening, because you never stop to think about things like that in your day-to-day life. But that kind of brought it home to me." (John, SHB)*

This grounded sense of self within the identity of their haemophilia and their perceived unique physical issues found conflict when needing to complete the outcome measure questionnaires. Whilst there was broad agreement that the time completing the questionnaires was acceptable, there was an observation that many of the measures included did not reflect them and their haemophilia. There was a feeling that they were being '*shoe-horned*' into certain responses (John, SHB) made worse by a perceived lack of sensitivity to their condition.

> *"It's like they're written by people who don't know haemophiliacs. A lot of that stuff is… I mean, you know how day-to-day haemophilia is in general, and especially in, I suppose, my cohort where we're dealing with haemo-arthropathy. You can have a good day and a bad day and they could be separated by ten minutes." (Luke, SHA)*

The concern for needing to know how to respond appropriately on the questionnaires brought some concern over trying to answer them, with a reflection of the previous responses and a worry that the answer would be somehow incorrect, bringing difficulty in working out '*what the truthful answer is on those things*' (Carl, SHA). Some participants were also mindful of the fact that whilst they had enjoyed participating in the study and got a lot from it, other physical ailments

(such as low back pain) meant that they would have worse scores at the end than at the start of the study.

> *"The one we filled in at the beginning, I was in a better place than I was… than I am now. So, the results on the questionnaire here are going to be… I'm going to be a lot worse than I was then, but it's not down to the exercise regime in any way. It's just down to where I am." (Liam, SHA)*

7.4.2.2 Subtheme: Seeing potential emerge

Whilst some of the outcome measures may have presented difficulty in reconciling the experience of participation with perception of change, a myriad of other changes appeared to be happening as a result of taking part in the study. The experience of pain during and after the study presented some with surprising insights to themselves and their relationship with it. The pain/physical activity relationship whilst an initial concern for some, developed gradually to an emerging sense of good change and positive reflection about the exercise activity.

> *"And less pain afterwards was a good measure as well. Being able to walk the next day was a good thing. Then I knew that I was working harder and I wasn't feeling as much pain the next day, so it must be a good thing." (Luke, SHA)*

For almost all participants, pain continued to be a feature in their life after the study ended, but there was a shifting relationship between its influence on their activity and how it made them feel about themselves.

> *"you kind of… it sort of carries the pain. I don't know how to put it. It's like the pain becomes a passenger as opposed to a driver. It's not the dominant thing that I'm thinking about now." (Adam, SHA)*

Reflecting on why this may have been the case saw some attributing such change to feeling stronger and fitter as a result of doing the exercises, and others reporting a confidence in their own physical ability. The inclusion of the knowledge and education components enabled others to take time to think about their own experiences and life with pain and begin to reformulate other options for management going forward.

> *"I suppose pacing, for instance… I still struggle with the pacing because if it feels good then I think, "Well, I'm ok now." But I'm starting to realise now that it's not necessarily the case… And understanding different types of pain*

was definitely good… But now I've realised there's a slightly different type of pain and I can still do some exercises with it." (Hugh, SHA)

Establishing a habitual behaviour for the study sessions and the progressive skill acquisition for the exercises themselves was seen as an important measure of change and improvement from being in the study.

"Yes, you're plugged into something. It makes a huge… a surprising difference, huge difference. Because you know that for that half hour, twice a week, you're committed to something and you've got to plug into it. It's having the structure of it." (John, SHB)

The consistency of the sessions and the unchanging order of exercise week on week meant that there was time and space to practice technique, eventually showing that this kind of approach could pay off.

"One example is that step punch thing. For a while, I found that very awkward and jerky and I thought… this was mentally not making sense. But then after a while you find a rhythm for it, and it's like, "Oh, yes, yes, now it makes sense. Now it's feeling like it's got going," kind of thing. That certainly happened with that exercise." (John, SHB)

Being able to feel change in themselves was a key feature of how participants viewed their participation week on week. Some took to counting the number of repetitions of the exercise they were able to do in the time week on week as a measure of improvement. Others noted a more general sense of feeling improved '*in terms of fitness and a general feeling of strength*' (Mark, SHA) through to seeing a definite change in their day-to-day function;

"I went to the football yesterday and I had to go in at the basement level at the Emirates and then go right to upper west three, third level. So, that's about eight or nine flights of stairs. I mean, it's a long way up, it's a big stadium. I got up to the top and I wasn't out of breath." (Adam, SHA)

The physical manifestations of improvement were also accompanied by an awareness of confidence to change and feeling better in themselves alongside positive changes in mental health and well-being.

7.4.2.3 Subtheme: Motivation and support

The study itself was delivered by specialist haemophilia physiotherapists known to the participants from their own previous clinical interactions. The delivery of the

study in this way was highlighted to be positive and enriching by both the physiotherapists and the participants.

> *"The actual exercise sessions – worked really well, and I think probably showed a slightly different side of physio, how physio can help people, that I hadn't done before… I think it has helped with that and has helped me understand them a bit more." (Liz, Physiotherapist)*

The support offered to participants by the physiotherapists in the study was shaped by these already established therapeutic relationships and was viewed positively, as it helped create a safe space for support, advice, and encouragement to participate fully in the study.

> *"I think it's made me definitely think about the pain, the types of pain, a bit more. And it just helps talking to Liz, I think, each week, because… Because I think… I do feel like I'm starting to understand the different pain a bit more and I'm getting a little bit more confident with what's arthritic pain and what's potentially a bleed." (Hugh, SHA)*

Even though the study was delivered completely virtually, the experience and knowledge of the physiotherapist, coupled with the trust in this relationship from the participants meant that advice about pain and support to continue could be safely given and received.

> *"I guess me having the confidence as well to say, "Push through it a bit, push through it a bit," and sort of knowing that… you know, "You've had treatment, we know these are your issues with your joints and that you may be experiencing some pain. But it shouldn't be bleeding." It's that kind of thing… you can only get that through experience." (Dan, Physiotherapist)*

Those participants who took part in the group exercise classes also found support from the experiences of other PWH like them, and so were able to reflect on those experiences in how they managed pain and negotiated day to day life with arthritic joints.

> *"I find it fascinating to get other people's experiences because it shows you you're not unique, that actually some of the things you struggle with everyone struggles with, and that's quite refreshing… I really enjoyed hearing other people talking about their own personal experiences because it chimed with me." (Mark, SHA)*

Even with the levels of enjoyment reported and the support received, there was a view that although a 6-week intervention is '*probably enough*', this was in part due

to the view that it was necessary for participants to find a way to continue with activities in their day-to-day life.

> *"I mean, six weeks twice a week is not going to produce anything dramatic physically. It's given me the incentive or the motivation to exercise again, because I'd slipped off the… So, this has helped get me back into exercising. And I mean, you know often it's just starting again and then it rolls on, hopefully it keeps going." (Luke, SHA)*

Participation in the study appeared to provide sufficient motivation and new skills for many to look forward to what they would now want to do following the end of the exercise sessions.

> *"Prior to that it was specifically focused on the knee or the ankles or whatever, whereas this has been the whole-body experience. It's a way of getting that impetus to kind of carry on and keep working on shoulders, which I wasn't really doing before. You know, I can open jam jars like anything now." (Liam, SHA)*

There was both an inspiration quality to the overall experience of taking part, but also a broader, more practical note to having acquired further skills that could be applied going forward to painful arthritic joints and physical activity in general. Having been shown that they could do more exercise than they initially thought, and that nothing negative happened as a result, facilitated this positive view of their immediate future at the end of the study.

7.4.3 Theme 3 – Future insights: acknowledging the present in future care

7.4.3.1 Subtheme: The virtual benefits

The virtual delivery method used in this study was viewed as overwhelmingly positive by participants. The nature of haemophilia care means that most people with haemophilia live long distances from their haemophilia centre, so the time saved by not needing to travel physically to the hospital was seen as extremely beneficial.

> *"It was convenience. I could do what I'm doing with you now by chatting over the phone and seeing… you know, actually seeing each other. So yes, it*

was a convenience thing. It seemed like a good idea, the fact I would be having a bit of a session and not having to travel for it." (Carl, SHA)

This limited burden on time and expectation of taking part in the study was also highlighted as a major reason to take part and even being able to do more if possible.

"Speaking honestly, if I'd done that two sessions in person at the end of the six weeks I would have been glad that it was over because I didn't need to keep going to the hospital. Whereas doing it virtually I could have carried on for a few weeks more because I was quite enjoying it. It's much easier to access doing it this way." (Adam, SHA)

Whilst there was some recognition of an ongoing need for face-to-face physiotherapy intervention, participants were able to reflect that a virtual approach also offered a similar option for those with impaired mobility and so being able to provide a more equitable approach;

"Maybe some people would prefer to come in for a face-to-face. I think that's the other thing about haemophiliacs. I suppose some of them… perhaps their mobility's not so good and it's a problem using public transport. And it's just… it's a whole lot easier. I know you don't have the person-to-person contact but it's not… it's not so different. The logistics are easier." (John, SHB)

The physiotherapists delivering the virtual sessions agreed with the sentiment of convenience and time saved for participants. However, they observed that for them, the logistics of organising the sessions for all participants across the six week period came with some difficulty in allowing for enough time to deliver a quality session to each person;

"Because it essentially takes up a day of work when you've got the six, because you've kind of… I was booking someone in for 10, someone 11, someone for 12 – you can't really do it much closer. You can't do them back-to-back because then you can't have a break in between, you can't… you can't discuss things with… you know… So, that's essentially an entire day." (Dan, Physiotherapist)

There was also some thought given as to how an approach such as this study could work on an ongoing basis to allow more people to access a programme such as this.

"Even with just… it was only four people but it took out the whole of my Monday afternoon – which is fine. But to do that long-term and then you're

only doing four people, how can you… You know, potentially, you would want to have a few more." (Liz, Physiotherapist)

It was not just the physiotherapists who were aware of the potential limitations of arranging time slots. Some participants were also mindful of the logistics involved in trying to arrange appointment times that would suit those in the study.

"Well, I mean, it was a bit of stretch sometimes... I don't think he could have done much more. He was offering slots, he tried to fit them in, people seemed to be able to find time." (Adam, SHA)

Unsurprisingly there were various technical failures experienced in the study, usually involving failures of Wi-Fi or technical issues with webcams. Even so, it was still viewed as being more advantageous than potentially missing appointments in real life due to travel delays, especially as such issues did not put people off and most were able to figure out a workaround.

"There were a couple of times when my Wi-Fi was off on my laptop and I was stuck on my phone, but… Yes, we just had a laugh about that, but that was ok. With modern technology… ok, maybe doing it on a phone isn't ideal but you can still do it." (John, SHB)

The physiotherapists were mindful of the potential limits of a wholly virtual approach, particularly regarding the limits of visual assessment of a joint/limb if issues were reported and concerns were raised. The challenges of progressing more technical exercises using only virtual means was raised as a potential future consideration as well.

"If exercises were a bit more complicated and needed a little bit more equipment and I needed to demonstrate things with more equipment, then I suppose that's when it would potentially be challenging." (Dan, Physiotherapist)

7.4.3.2 Subtheme: Expertise for support

The relative success of the telerehabilitation experienced in the study was linked to expertise based on well-established therapeutic relationships. Providing this type of novel physiotherapy intervention in the study also strengthened the view of what care could be.

"This really makes you feel like someone's listening and someone's caring enough to do something – rather than them pitching up every six months

and then saying what's wrong and there's a quick chat with everybody. So, that's another hidden benefit, is that you're feeling part of… you and the unit are feeling part of the same thing. Which is great." (Luke, SHA)

The mode of delivery and the continuity also provided the physiotherapists with a positive view of providing rehabilitation for the people they looked after.

"it was nice to just do a programme of… a programme of exercises with a group of patients, and have that continuity, that it wasn't just sort of random." (Dan, Physiotherapist)

The continuity and enhancement of already established relationships also allowed different ways of thinking about how to encourage ongoing participation in activity and exercises at the end of the study. Participating in the programme and newly forming habits created new ways of trying to plan in activity that was not necessarily in place beforehand.

"we talked about how he could take things forward, and he said, "Well, in my work diary I'm just going to put 'physio appointment', even if it's actually I'm going to the swimming pool." And I said, you know, "It's more beneficial for you to go swimming and do that as a physical activity, rather than coming to see me for a physio appointment, so in my mind that makes sense." That's something that we've got as a shared agreed goal." (Liz, Physiotherapist)

There was a positive sentiment from participants in trying to continue with exercise activity at the end of the study. Some planned to use the structure of the physiotherapy-led exercise sessions and look to source some small pieces of equipment such as exercise bands. Others were able to conceptualise activity plans they felt would want further support and input from a physiotherapist.

"I'll probably draft my exercise plan based upon what I've done, and then run it by [the physio], go through it all, go through the exercises, and then tailor it with a bit of detail. So it's partly knowing which muscles are supposed to be being worked, because you could do a squat in multiple ways and you can do a cheats version or you can do one that does the business." (Adam, SHA)

The need for ongoing input, advice and support whatever the choice of exercise or activity was prevalent throughout, further highlighting the need for supported care and input along a long-term timeframe, in keeping with the overall broader care provision model of haemophilia.

7.4.3.3 Subtheme: Future rehabilitation needs

Participants were enthusiastic about a future care model that included elements similar to that of the study they participated in. As previously described, the virtual sessions were highly regarded in creating an easier way to participate in exercise at home. The degree to which they enjoyed them came as a surprise to some with suggestions of a regular rolling programme of online exercise being established where people could drop in

> *"If the online sessions continued, even if it was once a fortnight or a lesser frequency, I'd certainly sign up for those because I thought they were… I found them really beneficial and I actually really enjoyed them." (John, SHB)*

The physiotherapists were able to appreciate the value the participants gained from this study with the virtual sessions. They were however mindful of more practical issues such as time needed to host them, concern about maintaining interest, and people dropping out, as well as concerns for how such a provision may influence self-efficacy day to day.

> *"I think you could definitely do more. But I think it was enough to get them started, in the hope that they will carry it on. But as I say, whether they will do… I think if you could have a rolling programme … But would you get people dropping out? I think you'd have some who would keep it going." (Liz, Physiotherapist)*

Participants were aware of the potential pitfalls of a rolling programme as well, noting that too many people with multiple different issues may be unmanageable for the physiotherapist.

> *"I mean, if you're going to go forward with it I don't know …"We do this, everyone's welcome, come and join in." Whether that would… I don't know how many people there would be, but if there was 30 people it might be difficult to manage 30 different sets of problems." (Liam, SHA)*

Ensuring equity of access and having a delivery structure that was more manageable for the physiotherapist was seen to be a possibility, if a model similar to others being used in NHS physiotherapy departments was considered.

> *"I think the 'Escape Pain' model, I think, would be the most effective because you get a committed group at the start – it's about the commitment at the start. I think that would be a key part of it." (Dan, Physiotherapist)*

Even though there was overall relative success of feasibility in conducting the study, the issue of the complex nature of PWH and their joint disease and pain was always

apparent. Being able to continue to provide a personalised approach for exercising with pain and haemophilic arthropathy means that the approach used in this study may not always be do-able.

> *"But I think if it had had too much personalisation you might end up with a bit of a free-for-all where everybody's doing something completely different." (John, SHB)*

Participants once again were able to attribute the importance of the established clinical relationship in personalising future meaningful interventions.

> *"The trick, I suppose is going to be knowing how to personalise it for each person. I mean, I'd had the Joe Wicks experience so I knew what… I mean, he ran through a lot of exercises over the time to keep the kids interested, I suppose, so I knew which ones I had in my arsenal. How you're going to personalise it is going to be down to you knowing the patients, I suppose, and whether or not the patients have done any exercise before." (Luke, SHA)*

The physiotherapists noted importance of being able to identify and measure outcomes, but set against the complexity of the range of people that may benefit from interventions such as this in the future.

> *"It would have to be individualised. So, for one chap it might be a balance/falls type something, whereas for somebody else it would be something completely different. But I think that should be a standard. Rather than doing the HJHS, I think you should have a group of six or eight different outcome measures that you pick the best one for your individual patient." (Liz, Physiotherapist)*

However, the desired end result, whatever the approach and the people involved, was that everyone who could and would participate would feel supported, encouraged and safe to integrate exercise activity as a potential way of managing some issues of their ongoing pain into their day to day life.

> *"I hope that for all of them that they can see these exercises as things they can just do at home. And hopefully, by doing it with them over a six-week period, they can see that it's something that you can just sort of slot into life – it doesn't have to be that you have to go to the gym." (Liz, Physiotherapist)*

7.5 Part 3 - Integrated display of quantitative and qualitative findings

Whereas quantitative and qualitative data have been presented in a narrative approach to this point, this section will present both datasets in a side-by-side format to integrate points of interest. As previously described in Chapter 2, the level of consensus between the datasets will be described as:

- Confirmation – the findings of both agree
- Expansion – the data diverges and expands insights or describes complementary aspects of the topic at hand
- Discrepancy – the data appear to contradict each other or are inconsistent

7.5.1 Feasibility

Table 29 presents the integrated findings related to study feasibility.

7.5.1.1 Recruitment to the study was feasible

Recruitment approaches to the study were adequate with both the method of delivery and the content being of interest to those PWH approached. The perceived relevance of the study contents to participants alongside convenience of virtual delivery appears to have positively facilitated decisions to take part.

7.5.1.2 Fidelity to the study protocol

Fidelity of delivery of the study appeared to be compromised by the use of telephone delivery instead of visuals on webcam. However, it was clear that for those who participated using the telephone, this method was feasible in delivering the verbal instructions needed to participate and was acceptable in terms of study burden and ease of participation. This highlights that whilst using virtual delivery methods (webcam on MS Teams) was feasible, further investigation is needed to clarify the potential positive effect on inclusion and equity of using only verbal communication via telephone.

7.5.1.3 Participating in the study was safe

Overall, the data confirms that it was safe to take part in the study, with those adverse incidents recorded being non-severe in nature and not preventing ongoing participation in the planned sessions. Participants reported feeling safe to do the exercises prescribed in their own homes. The responsibility to self-assess for any

potential need to treat with any extra clotting factor was theirs and was not viewed as a burden. Feelings of safety were enhanced by being able to alter and modify exercise techniques to suit individual physical requirements.

7.5.1.4 Study burden

The burden of participating in the study was acceptable, with good attendance recorded for most attending the individual exercise sessions, although the postal return of outcome measures at study end was inconsistent, with three participants failing to return questionnaires at T1 and four non returns at T2. Interestingly, the three people that did not return the questionnaires at T1 did agree to be interviewed, suggesting that techniques for collecting post intervention outcome measures may need to be reviewed in further studies. Whilst burden for the participants appeared acceptable, a burden of study administration was highlighted by the physiotherapists. Whilst the organisation and delivery using MS Teams was viewed positively, the time required in the working week to deliver the study was significant. It was just about manageable for the physiotherapists to deliver the sessions, but there were concerns about making time for other aspects such as note writing. The therapists did note that 5-6 people would be the maximum that could be feasibly included in the study. These comments highlight that whilst the study delivery is feasible, time in normal clinical workload is limited and so this may well be a limitation of feasibility in haemophilia centres with limited physiotherapy time.

Table 29: Integration of Feasibility findings

Topic/Domain	Quantitative findings	Qualitative findings	Level of consensus
Recruitment	Of the 13 people approached to participate, 10 agreed - Consent rate = 77% - Recruitment rate = 90%	**(Carl, SHA)** – "*It was convenience… It seemed like a good idea, the fact I would be having a bit of a session and not having to travel for it."* **(Bill, SHA)** – *"The biggest thing that piqued my interest … with this it was a little bit more… well, we can hit it [pain and multiple affected joints] from all angles."* **(John, SHB)** – *"It sounded like an interesting programme and I thought it would be doing something positive as well, kind of giving something back. I didn't know if the exercises… I looked at them and I thought, "Well, I'm not sure if they're going to work or not, I'll give it a go."* **(Mark, SHA)** – *"I liked the idea of having routine exercises, and I hoped that it would kickstart me into doing something a bit more structured each week."*	Confirmation
Fidelity	The intervention was delivered virtually using webcams 80.4% of the time. 12 sessions were delivered using only the telephone	**(Liz, Physiotherapist)** – *"There were a couple of people who we did that on the phone rather than having a camera, but that's just… one chap it's just not… that's just not his thing. You just have to take their word for it that they're doing the right thing"* **(Bill, SHA)** – "*I always did it over the phone. Not because I have a problem with group sessions or anything like that – I was more of a difficult patient because I do shift work. So, the phone calls were easier."* **(Mark, SHA)** – "*And if the worst comes to the worst you can always switch off the video – you don't have to see people. The important thing is actually hearing the*	Expansion

		physio going through the programme and timing you and saying, "Three, two, one, start," and then telling you when the 30 seconds was up" **(John, SHB)** – "*There were a couple of times when my Wi-Fi was off on my laptop and I was stuck on my phone, but… Yes, we just had a laugh about that, but that was ok. With modern technology… ok, maybe doing it on a phone isn't ideal but you can still do it."*	
Safety	Seven incidents reported whilst in study and were evaluated as non-serious: - Increased joint pain (n=4) - Joint bleed (n=1) - Muscle pain/ sprain (n=2) No serious adverse events were reported.	A feeling of safety whilst participating was supported from the interview analysis and evident in Theme 1: **(Jack, SHA)** - *"I find them quite safe doing them and not… I mean, even before I was always doing some kind of exercise."* **(Luke, SHA)** – *"I think I did treat out of prophylaxis once, and that was for… the thigh was really sore. I thought, "Let me treat so that it doesn't mess with the routine. If it is a bleed or if it is something more than just tautness, let me treat this."* **(Hugh, SHA)** – "*So I felt… yes, I definitely felt safe with doing them – just changed them [the exercises] if need be."* **(Liam, SHA)** – *"For the squats and the lunges I had a chair next to me that I could hold onto… it was there, just a kind of confidence thing, really. So, yes, it felt safe. I had plenty of room around me"*	Confirmation
Attrition	Seven of the 10 participants completed the outcome measures at T1 and 6 completed them at T2. Nine of the 10 participants agreed to be interviewed at the end of the study		Silence in qualitative data

	No-one withdrew from the study		
Adherence	Attendance and participation across all sessions was 68% Participation in individual sessions was 84.5% Participation in group sessions was 52.1%		Silence in qualitative data
Study Administration		**(Liz, Physiotherapist)** – *"There was a lot of… obviously, the admin side of it, but a lot of that is just because it's a study. Because I was thinking, practically, how could this work if you do it outside of a study."* **(Liz, Physiotherapist)** - *"I had them each hour and that was enough time for me to then do the little bit of a start, do the main session, say goodbye, do the notes, do the next one … you needed that hour to do the admin bits either side. Yes, 45 minutes would have been stressful to do all five in a one till five chunk of time."* **(Dan, Physiotherapist)** - *"It does take up quite a lot of time doing it that way… I got quite lucky with the participants, that once I had them in and we just said, "Ok, well, this is what we're going to do and these are the proposed dates. How does that work for you?" there was really hardly any issues with all six of them."* **(Dan, Physiotherapist)** - *"Six would be a… six would be, I would say, an absolute max. So, it would be doable with enough planning, but I think it would be a challenge. Because it essentially takes up a day of work when you've got the six"*	Silence in quantitative data

7.5.2 Acceptability

Table 30 presents the integrated findings for acceptability of the study.

7.5.2.1 Acceptability of study protocol - delivery

Quantitative data was not available for many of the domains relating to acceptability of the study. The virtual delivery of the program was positively received by both participants and the physiotherapists. Using digital platforms such a MS Teams was viewed as normal now following the effects of the Covid-19 pandemic, and came with the added advantage of saving time on travelling to and from hospital. However, there was still a desire for options involving physical face-to-face, associated with perceptions of completeness of assessment and seeing the whole person. Further consideration will need to be given to finding a balance or blend of virtual and physical face-to-face to ensure the needs and expectations of participants are fully met.

7.5.2.2 Acceptability of study protocol – exercises

The exercises described and performed in the study were acceptable to participants and the physiotherapists alike. The six-week programme was acceptable as physical skills improved, although the timings between the sets was felt to be too long and left participants wanting to get on with the next set of exercises. The general, whole-body approach of the programme was beneficial, in that it provided a positive effect to cardiovascular activity as well as being seen to target multiple body areas. However, as the weeks progressed, having a more targeted approach to their own self-identified problem joints was preferred, with some wanting to spend their time on joint specific activity. The complexity of facilitating a general exercise programme in those with multi-joint arthropathy against an identified problem joint may provide further challenges to acceptability of an approach such as this.

7.5.2.3 Acceptability of study protocol – group sessions

The knowledge and discussion group sessions were delivered as described in only one study site, due to a lack of attendance with the online group sessions at the other. For those that did attend the sessions, the experience was underwhelming. Even though there were some topics that piqued interest in individuals, overall, the

sessions did not enhance the experience of taking part in the study. However, it was apparent that topics covered in the sessions did have some influence on thought processes pertaining to that topic on an individual level. Those that did not join this group online had some of the information from these sessions discussed with them by the physiotherapist, where it was received well. Whilst attending the sessions was acceptable to those that participated, the perceived low value of the content and the lack of engagement by one cohort highlights the limited acceptability of this aspect of the study protocol. Further consideration as to the need for and inclusion of knowledge or education sessions will be required.

7.5.2.4 Acceptability of outcome measures used in study

Although the time to complete the outcome measures used here was acceptable, it was evident that measures themselves had limited value to the participants. Many reflected that measures such as these are a regular feature of routine care provision, as well as being part of other treatment related studies that they may have taken part in previously. Rather than being seen as helpful, this familiarisation appears to limit the perceived accuracy of how they are completed, with answers given little thought. The questionnaires' lack of specificity to them, their condition and their current experience was frequently reported. This raises the issue of how relevant the results obtained from such questionnaires may be when trying to evaluate efficacy as an outcome, and further highlights the need to consider other approaches or tools.

7.5.2.5 Enjoyment and motivation

The high degree of acceptability of the study was reflected in the positive reports of enjoyment. The physiotherapists observed that participants appeared keen to participate and enjoyed the sessions. Participants noted that seeing others like them and feeling like they fitted in, also helped their overall positive experience of the study. The individual awareness of the physical and psychological effects of the exercises also helped facilitate their enjoyment at taking part. Motivation was also positively influenced, whereby some felt a change in their confidence to do more, and positive behavioural action enabled others to plan out future exercise activity that involved equipment.

Table 30: Integration of Acceptability findings

Topic/Domain	Quantitative findings	Qualitative findings	Level of consensus
Protocol – virtual delivery		**(Carl, SHA)** - *"that makes a big difference. That it can be virtual, you literally can… you can switch on your… switch on your link whilst you're at work with a half an hour and get it done, and then… It's not like that if you have to get in the car and drive and get back and all of that stuff"* **(Liam, SHA)** – *"I mean, it works and it doesn't impinge on your day, as it were. If I was coming up to you, it's an hour to you and an hour back again, so that would be a morning gone. Whereas doing it this way, it's an hour roughly, 45 minutes or whatever, and then you get back and you're at home and you get on with doing what you want to do. And that really worked, I thought."* **(Jack, SHA)** – *"I think in the past couple of years we're doing the same thing for everything. We're in front of a screen now and you just become… like, again, more normalised. It's not much different, really, I suppose."* **(Luke, SHA)** – *"I suppose turn on the camera, do your thing, 40 minutes later you go and get on with the rest of your day – not two hours later you get on with the rest of your day, or two and a half hours later you can get on with the rest of the day. I mean, even for me to get to the Royal Free, it's 45 minutes or something – get to the station… or if I drive, even… So, that's an hour and a half each way, maybe. This is obviously more convenient."* **(Adam, SHA)** – *"face-to-face is better, in that you get much… Certainly the personal face-to-face session, you really… You can't convey the full physicality of what you're doing on a Teams call."*	Silence in quantitative data

Protocol – Exercises		**(Liz, Physiotherapist)** – *"But I think just that general conditioning and general fitness was something that was quite… it was within everybody. I think so many people who we see have not been able to do what they want to do because of pain or for whatever reason haven't pushed themselves. So, I think it fits when it's very generalised."* **(Carl, SHA)** – *"We had tailored it more to just to some… They were still doing a couple of the other movements because… you know, it's good to get you panting and your heart rate up, so we were doing some of the other ones which was good as well. But by the end of it we were doing more targeted stuff for my… you know, for my ankle."* **(Adam, SHA)** – *"I think six weeks is just about right. It allows people to learn as they go along. It allows for the odd session that you have to miss. So, it's a good length of time. I'm happy enough with that."* **(Mark, SHA)** – *"Thirty second rest between each… I'm not sure what the right… set, between each set. The two minutes between each exercise, each set of exercises, I felt was probably a bit long. You could probably get away with a minute, or a minute and a half. Some of us were sort of twiddling our thumbs a bit for two minutes."* **(Dan, Physiotherapist)** - *"I think they were good because they had to be… they seemed like they were covering the key areas that these guys need to work on. I think the… there were certain ones… It's always going to be this way. There were certain ones that, for some, some of them they just weren't… they just weren't finding them particularly tough."* **(Jack, SHA)** – *"I think it was quite comprehensive, really, for different parts of the body. For me, as I said, it's just getting that heart, that intensity, it just feels good. It doesn't matter what exercise you do."*	Silence in quantitative data

Protocol – Knowledge and discussion sessions	Only one of the two sites was able to complete the knowledge and discussion sessions alongside the group exercise sessions – though the information in the slides were discussed with participants outside of the session description in the protocol	**(Hugh, SHA)** – *"It didn't… well, it didn't actually happen, really. I think there were technical issues and also when I was going to join them I think… well, basically no one else was left."* **(Liam, SHA)** – *"The slides were interesting as well because it just kind of gives you a reminder of what you're doing and what to look out for and that kind of thing. And knowing your limits and then perhaps after a few weeks just trying to push those limits"* **(Luke, SHA)** – *"I can't dismiss it because I'm sure that there were moments in each PowerPoint where it was like 'yes'. And even if that's a personal back of the head 'yes' and you're identifying with something, so you're feeling this person gets it, that's very valuable. I don't think any of it was revelatory."* **(John, SHB)** – *"Because a couple of the points he made… a couple of points that were in the slides kind of rang a bell with me and kind of resonated. I thought, "Yes, that is right, that's my experience."* **(Adam, SHA)** – *"and effects on wellbeing, things like that, that was interesting. And the link being made to pain and to management of pain was interesting. I'm not absolutely sure whether that's awfully different for me over the six-week period"* **(Hugh, SHA)** – *"I still struggle with the pacing because if it feels good then I think, "Well, I'm ok now." But I'm starting to realise now that it's not necessarily the case. But the pacing was good. And understanding different types of pain was definitely good"*	Discrepancy
Outcome measures used		**(Carl, SHA)** – "*I mean, a lot of those surveys do feel, you know, quite kind of generic. And you know, on a scale of 1 to 10… I bet they differ every time I fill them out. You know, I think about that every time when I'm filling them out and go, "God, what did I put last time and is it different?"* **(Luke, SHA)** – *"Some of them I had to answer… like, "How did you feel in the last 24 hours?" "I felt shit. I wasn't able to walk," kind of thing. Whereas that wasn't really a*	Silence in quantitative data

		picture of the last three months. It does squeeze you into answering in a particular way which might not be relevant on the whole." **(Adam, SHA)** – *"They weren't precise enough. I mean, they were sort of flopsy questions, really."* **(Jack, SHA)** – *"I answer similar questionnaires as this all the time, over the years, it's just the same to me how I answer them, really."* **(Mark, SHA)** – *"They took me about… I don't know, 15 minutes to go through. They weren't terribly onerous. There was one… Some of them are a bit vague."*	
Enjoyment		**(Dan, Physiotherapist)** - *"I think it was… like, from the start, from quite early, it seemed like there was… it felt like a positive thing. So, it felt enjoyable for me and I got the sense from the participants that they were enjoying it and benefiting from it as well. So, it made it an enjoyable experience."* **(Luke, SHA)** – *"It was very useful, it was very beneficial. I could see a need for it, I could see a desire for it, even if the person is not necessarily aware of the desire for it. I felt good doing it. I'm glad you did it and I'm glad I was able to be part of it."* **(Jack, SHA)** – *"I felt really relaxed. I didn't have to think about… concern about anything. But in a different situation with different people, then you wouldn't be able… you always think about "I'm different to them". And definitely, it makes you just relax a lot more and just get on. Definitely you feel more enjoyable doing it."* **(Adam, SHA)** – *"It was nice. Good to see other people a remarkably similar age… and the experience is so similar, really, you know, for everybody."*	Silence in quantitative data
Motivation		**(Hugh, SHA)** – *"it was good to take part and it's helped me, I think, get more confident and get out of… I think there was a little rut and I think that should help me stay out of it and get a bit more consistent with some of these exercises. So, it was good to take part, yes."*	Silence in quantitative data

		(John, SHB) – "*I think my plan is that… Because I've got an exercise bike that I kind of go on, so I thought if I did alternate days, one day on the bike and one day running through those exercises – that would be the plan, anyway – I'd do that."* **(Luke, SHA)** – *"This has helped get me back into exercising. And I mean, you know often it's just starting again and then it rolls on, hopefully it keeps going."*	

7.5.3 Efficacy

Table 31 presents the integrated findings for efficacy of the study.

7.5.3.1 Efficacy findings

There were small changes in outcome measures related to pain across the group. Only one participant demonstrated a change in keeping with a minimal detectable change for pain interference on the BPI, with two participants having a similar change for the PSEQ. Taking such results in isolation would suggest little effect of the intervention on the pain experience. However, the qualitative data provides deeper, more contextualised findings relating to pain in the study. There was a consensus that whilst the presence of pain overall did not significantly alter, its potential negative influence on day-to-day activity was positively moderated by participation in the study. This change in awareness of pain daily was a surprising outcome and one that was welcomed by participants.

Similarly for function, the qualitative data help expand and further quantify that collected in the outcome measures. Only one participant reached an improvement in the HAL questionnaire associated with a minimal detectable change. There was benefit in observing others in the group setting, helping quantify their own functional issues against those similar to them. Improvements in daily functional activity were noted but had not been identified in the PSFS as activities that individuals wanted to change. There appears to be functional improvement which is only observable to participants after taking part in the exercises. This suggest that in some cases, upfront identification of functional goals prior to commencing an exercise programme may not always highlight activity that has the potential to change, or the self-belief that such change is possible.

Measures of quality of life showed little change across the group, however qualitative findings indicate change that was positively received. Participants valued the surprising effect on their aspects of their quality of life, particularly about how it made them feel in their body. The very individual, context specific improvements highlight further the difficulty in identifying a goal to change if one is unsure it can change.

Discrepancies between the one question PGIC and the qualitative findings highlight that a more complex view of change and improvement exists on an individual level. There was a theme of feeling better in themselves from participating. This uplift was for some a sense of physical change, others noted improvement in mood. Having a routine positively influenced perceived personal improvements, even though in some cases individuals were not necessarily aware initially that such an approach could be beneficial.

7.5.3.2 Behaviour modifications

Whilst the protocol was conceived to include behaviour change techniques in the design, there was no specific quantitative measure to evaluate this. The inclusion of BCT's to encourage participation appears successful. Participants however did note a desire to change or actively change being ready to continue to exercise. Some had already diarised ongoing exercise sessions to do independently, though there was trepidation as to how long his may last. Such findings indicate a positive reflection on the decision to design the protocol incorporating BCT's, and together with the other efficacy findings, would suggest that this has been a positive outcome.

7.5.3.3 Behaviour change techniques

The overall study design included a range of behaviour change techniques as previously discussed in chapter 5. Of the 21 BCT's identified within the overall study design and delivery, analysis of the qualitative data highlighted five that were most commonly coded from the dataset. They were:

- Action Planning
- Credible Source
- Information about health consequences
- Self-monitoring of behaviour
- Goal setting (behaviour)

Table 31: Integration of Efficacy findings

Topic/Domain	Quantitative findings	Qualitative findings	Level of consensus
Pain	BPI domains: *Worst pain, least pain, pain now:* Group: no change in group median *Pain interference:* Group: median decrease of 1.58 points Individual: increase (n=3), decrease (n=4) PSEQ: Group: median decrease of six (worse) Individual: - Unchanged (n=1) - Worse (n=3) - Improved (n=3)	**(Adam, SHA)** – *"What I mean by that is it's not so much the pain is necessarily less, it's the confidence with which you can cope with it has improved."* **(Bill, SHA)** – *"I've got… It's just less pain. All the pain is less, if that makes sense. The pain is a little less. It's still there but… Like, for example, bending … that kind of movement is now not sparking as many issues."* **(Adam, SHA)** – *"you kind of… it sort of carries the pain. I don't know how to put it. It's like the pain becomes a passenger as opposed to a driver. It's not the dominant thing that I'm thinking about now."* **(Carl, SHA)** – *"It's always maintained the same, my pain is consistent. So whether I felt any extra pain after doing the exercises – no more than I normally would from doing those kind of exercises, which I've done my whole life. So there was nothing… no difference in pain to report over the six weeks period"* **(Luke, SHA)** – *"And less pain afterwards was a good measure as well. Being able to walk the next day was a good thing. Then I knew that I was working harder and I wasn't feeling as much pain the next day, so it must be a good thing"*	Expansion
Function	HAL: Group: Small increase group median of 5.4 points	**(Hugh, SHA)** – *"It does make you realise that it's one of those things where the strength of your body will help with the arthritis. I think that's something I didn't really consider that much, whereas now I'm a bit more aware of it."* **(Adam, SHA)** - *"I went to the football yesterday and I had to go in at the basement level at the Emirates and then go right to upper west three, third level. So, that's*	Expansion

	Individual: Increase in total score (n=5) (n=1 change associated with smallest detectable change), decrease in total score (n=2) PSFS: Group: no change Individual: no change (n=2), deterioration (n=2), improvement (n=3) (n=1 achieving change associated with MID)	*about eight or nine flights of stairs. I mean, it's a long way up, it's a big stadium. I got up to the top and I wasn't out of breath."* **(Mark, SHA)** – *"Well, it was just showing me that actually I… I find certain things difficult to do and I realised that they all find them difficult to do as well, so it's not just me being particularly bad."* **(Jack, SHA)** – *"But it definitely helped my… I mean, I can tell when you breathe, I know how much the intensive… you know, for the health of your lung and your heart, definitely it's there, and I can tell that"* **(Adam, SHA)** – *"There's still a bit of pain going upstairs – the most tangible thing that's improved is going up and down stairs with both legs as opposed to one… using my left leg only and my right leg, with the weak quads and things, the one where I had the knee replacement… So, I just feel more in control of it. And your balance is a little bit better"*	
Quality of life	EQ5D5L Group: VAS showed increase group median of 5 points, Utility score showed decrease in group median by 0.26 Individual: VAS score increased for 2 people and decreased for 4 people Utility score improved for 3 people and decreased for 3. MSK-HQ	**(Adam, SHA)** – *"It really opened my eyes to how important it is, how quickly it can make a difference to your body. And I just wish I'd been doing this much earlier."* **(Luke, SHA)** – *"This really makes you feel like someone's listening and someone's caring enough to do something –that's another hidden benefit, is that you're feeling part of… you and the unit are feeling part of the same thing. Which is great."* **(Liam, SHA)** – *"I feel better… I mean, for exercising. And I think the process of doing the exercising is good mentally and afterwards you feel "Yeah, I've done it."*	Discrepancy

	Group: Increase of nine points in group median Individual: 5 people had improvements, but only one with significant MCID.		
Subjective view of improvement	Patient Global impression of change (n=7) - Worse (n=1) - No/minimum change (n=4) - Much improved (n=2)	**(Luke, SHA)** – *"It was very useful, it was very beneficial. I could see a need for it, I could see a desire for it, even if the person is not necessarily aware of the desire for it. I felt good doing it. I think it would be useful to me."* **(John, SHB)** – *"And there's no doubt that if you're doing structured exercises they have a positive impact on your wellbeing and your health because you get more adept at doing them, then you can have more of an exertion because you're putting more into them, and you do… it does uplift you that kind of physical activity"* **(Mark, SHA)** – *"I just feel so much better doing the exercise. It's really woken me up to the benefits of a simple exercise routine on a regular basis."* **(Adam, SHA)** – *"I think I do feel a bit bouncier. And that has effects on mood as well as your general… the mobility that goes with greater fitness. It's not that it's affecting the target joints particularly; it's more that it's affecting everything around it."*	Discrepancy
Behavioural modifications		**(Liam, SHA)** – *"Yes, it's probably given me a bit more impetus, again, to do more now I've been shown… you know, doing exercises at home and ways of doing it and different types of exercises."* **(Carl, SHA)** - *"To be honest with you, I could be doing more." And she said, "Right, ok, cool." And so I said, "So, you're all right if I just do more… obviously not pushing*	Silence in quantitative data

		it or going to crazy levels, but just… If you're in a position where you can do your exercises…" So, I did it every other day." **(Liam, SHA)** – *"I'm quite keen, actually. As I say, I've done it twice more since last week and scheduled another one in for tomorrow"* **(Jack, SHA)** – *"at the moment, yes, I still have that enthusiasm and want to do it and get on with it and do something about it. But in a month, two months later… I can't say anything."* **(John, SHB)** – *"Since the programme finished – it was only a week or so ago, a couple of weeks ago – I've tried doing some of those exercises on my own because I think they're worth carrying on with"*	

7.6 Discussion

The results of this study confirm that it is feasible and acceptable to deliver an exercise based telerehabilitation intervention for PWH who live with chronic pain. Whilst the outcome measures used in the study provided little quantitative evidence of clinically relevant changes in pain, function, and quality of life across the group, the post-intervention participant interviews highlighted domains of improvements that were not evident in the chosen questionnaires. Attendance and adherence to the individual sessions was universally acceptable, whilst the group sessions were more dependent on personal preference. Further feasibility work is likely to be required to ascertain how to measure more meaningful outcome measures, as well as the most effective and efficient methods of delivery of the intervention to ensure equity of access and managing the burden of delivery on the physiotherapists.

7.6.1 Feasibility of the intervention

7.6.1.1 Recruitment

Both sites were able to successfully recruit to the study. The estimation for recruitment was based on a figure of people attending for routine clinic review. In reality the recruitment approach was done across routine consultant-led clinical reviews (face to face and virtual) as well as in diarised physiotherapy appointments. Haemophilia is a nationally commissioned service by NHS England and the service specification states that those with severe and moderate haemophilia must receive a twice yearly clinical review (367). For future definitive trials, it is realistic then to assume that most potential participants would be seen in clinic within an 8-month period and so recruitment would be achievable.

7.6.1.2 Participation

Consenting to, and participation in the study exercise activity was feasible. The participant interviews highlighted that the study content was of personal interest to participants. There was also a sense of altruism in the potential benefits of the study to others in the future. Participants were highly trusting of the study by virtue of the fact that it was presented to them and delivered by a physiotherapist that they knew and trusted. These findings are reflected similarly in reviews that have sought to identify reasons why people participate in healthcare research (368, 369). Ongoing engagement and participation in the sessions were associated with feelings of

enjoyment. Participants also noted an improvement in their physical capabilities and seeing a positive change in their sense of self and in day-to-day activities relevant to them. Teo and colleagues conducted a recent review looking at the factors contributing to patient engagement in exercise rehabilitation within a framework of behavioural analysis informed by COM-B (370). They found that capability to take part was influenced by perceptions of exercise, skills to take part and knowledge of benefits to health and on individual health conditions. Lack of access to resources was a barrier to opportunity to take part, whereas having the time and social support to take part facilitated engagement. Positive health outcomes and enjoyment were seen as incentives for motivation. Consideration of an individual's previous experiences of exercise was felt to be an important clinical strategy to enhance engagement. The stakeholder involvement approach used in this study to develop and inform the study protocol appears to have been successful in creating an intervention that participants wanted to engage with.

7.6.1.3 Safety

The study was demonstrated to be safe with no serious adverse events recorded, and participants being unanimous in reporting they felt safe taking part. This is in keeping with findings of a recent Cochrane review of general exercise for people with haemophilia (371). The perception of being or feeling safe was not impaired by the virtual delivery of the study, as participants felt happy to do the exercises in the comfort of their own home environments. The strength and quality of the relationship between the physiotherapist and participants also appears to enhance and embed a sense of safety with virtual delivery of rehabilitation.

7.6.1.4 Burden

Participants reported minimal burden to taking part virtually. The physiotherapists however, noted an administrative burden associated with the time needing to be set aside from their clinical diary to deliver the telerehabilitation sessions. This is an important factor if other haemophilia sites were to be considered for future studies. The two participating sites in this study provide a full-time physiotherapy service in the haemophilia centres, however this is not standard of care nationally. In 2020, a national peer review of haemophilia services across the UK found that up to 60% of PWH have little or no access to specialist physiotherapy (372). The intervention

described in this study is based on the presence of both physiotherapy time and expertise to deliver it, and so there may be limitations to the feasibility of this study in its current form being delivered in those centres lacking an adequate physiotherapy service.

7.6.2 Acceptability of the intervention

7.6.2.1 Virtual delivery of intervention

The delivery of this study as a telerehabilitation approach was acceptable to both the participants and the physiotherapists. The onset of the Covid-19 pandemic in 2020 resulted in the accelerated integration of telehealth methods in providing ongoing care to PWH. Reviews of this technological implementation in haemophilia have been mostly positive particularly in being able to provide routine reviews and follow up and ongoing support for patients (346, 373).

The remote delivery of physiotherapy via telerehabilitation has been used prior to the Covid-19 pandemic. This has mostly been for the delivery of rehabilitation interventions for musculoskeletal related conditions such as low back pain, orthopaedic surgical follow up and neurological conditions such as multiple sclerosis, where its use has been shown to be comparable to in-person appointments and better than no treatment/intervention at all (179). A further review of a large number of RCT's also showed that exercise intervention delivered via telerehabilitation approaches (video consultation or telephone) was a viable alternative to in-person attendances for treatment of pain, function and quality of life impairments associated with physical disabilities (374). A recent study investigated the clinician experiences of using telerehabilitation for patients with OA knee. The intervention consisted of patients being sent an information pack via WhatsApp (self-management information, education materials and the exercises) with a follow up telephone call once a month by the physiotherapist. They found that whilst clinicians acknowledged the time and convenience benefits for patients, there was concern about perceived low value care by patients. There were issues also about communication and lack of physical assessment for reassurance of both parties associated with only being able to use the telephone (375). This point is interesting, in that those participants who took part using only the phone in this study noted no issue with quality or input. It is plausible

that the already established relationship with the physiotherapist may have positively influenced their view on the value of the telephone call over face to face on webcam.

7.6.2.2 Telerehabilitation in haemophilia

There is a dearth of evidence or published experience about the use of telerehabilitation approaches in haemophilia. One very recent study sought to qualitatively understand the experience PWH in a telerehabilitation programme delivered via WhatsApp using the video/camera functionality (348). The intervention was described as being a single weekly 30 minute 1:1 session of virtual, physiotherapy-led exercise session on camera with participants expected to do two further exercise sessions at home independently. The exercise plans were co-ordinated by the physiotherapist and included upper and lower limb exercises and education (the content of which was not included). The authors provide no quantitative data on collected outcomes, the number of participants, nor over what time period the intervention took place. Similar to the findings in this study, the authors noted a high degree of acceptability of this approach from their patient group. Time, convenience, and access to care delivered by a professional with expertise in the nuances of haemophilia was highly favoured. Some however felt that an in-person appointment would have been beneficial for their confidence to do the exercises, and others feeling that 30 minutes was not enough. Such views appeared to be influenced by the participants previous amount of experience or contact with physiotherapy prior to this approach. These findings when taken alongside the findings of this study, provide an encouraging view of the potential value of a telerehabilitation approach. It is clear, however, that further development work is required to ensure equity of access and what components of remote/virtual delivery may be most effective and valuable.

7.6.2.3 A Credible source

The delivery of the study by a physiotherapist known to the participants was highlighted as an important and valuable aspect. Outcomes for PWH appear to be better when they are managed in specialist haemophilia centres that provide a full multi-disciplinary team that includes a physiotherapist (376). The findings of the qualitative study in chapter 4 described the importance to PWH of healthcare professionals knowledgeable in haemophilia. This point is reflected in other studies

investigating the views of people living with rare disease, whereby trust and value in the care received is also positively influenced (377, 378).

More recent work on trying to elucidate the qualities of a good physiotherapist have shown that therapeutic relationships are established when responsiveness, communication, competency and collaboration qualities are observed to be present by patients (379). Long term care in rare diseases also breeds friendship and trust in that therapeutic relationship (380) which can in turn positively influence treatment satisfaction and more beneficial health behaviours by patients (381).

The premise of this study's design and implementation was to ensure delivery by a physiotherapist known and trusted by the participants and in turn was highly valued and acceptable to participants. Whether such a delivery model is feasible for haemophilia centres with limited physiotherapy time or indeed if this intervention would be as effective if delivered by a non-specialist is unclear and would require more extensive evaluation studies.

7.6.2.4 Content

The low impact, moderate intensity progressive exercise plan was acceptable and enjoyable for participants. This approach to the exercise programme was directly influenced by the findings of the qualitative study (Chapter 4), and with the input of stakeholders from the theory of change process. The tendency for an increased number of haemophilic joints to be present in older men with haemophilia highlighted the need for a whole-body approach to exercise. Such an approach should enable a sufficient challenge to the cardiovascular system, without the need for increased impact on the joints of the lower limb.

A Cochrane review investigating exercise interventions and patient beliefs for people with hip and knee OA reported that interventions are improved for participants if they are tailored to an individual's preferences, abilities and needs. This approach, alongside reassurance and clear advice, helps promote enjoyment and encourages participation (382). Some of the younger men in this study however, wanted a more tailored, joint specific programme. This highlights some potential limitation to the approach used here in younger people living with one or two problem joints (as opposed to four or more). Appreciating and understanding this person-centred,

individualised approach to exercise intervention is also important in facilitating longer term adherence in day to day life (383). Further studies may need to consider if designing a further, homogenous approach is necessary for those with less affected joints or if more specific, personalised exercises can be included in a programme design such as this.

The threshold of acceptability of the knowledge sharing and discussion sessions does not appear to have been met. Only one study site managed to conduct the session as described in the protocol, with the other study site being unable to deliver the sessions dues to lack of participation with the group sessions. Similar to the exercise programme, the content of the knowledge sharing, and discussion sessions was informed by the developmental qualitative study and theory of change process. Studies that have included condition specific education sessions have been included alongside physiotherapy interventions such as manual therapy and exercise, although none have been evaluated for effectiveness within those studies (242, 247, 252). One study compared the effect of an information DVD and booklet against a booklet alone on motivation towards better self-management of pain in PWH. They found the DVD and booklet had more impact on behaviour than the booklet alone, although there was no evaluation of participants views of the content itself (267).

Cochrane reviews evaluating patient education in both RA and OA have shown only small short term effects for disability associated with RA (384)and no improvements in self-management skills, function or quality of life in OA (385). However, the recent EULAR guidelines recommend patient education not as a standalone intervention, but as part of a broader multi-faceted approach to the management of arthritis (100). This component of the REMAP-Haemophilia intervention will require further evaluation and refinement if it is to be considered in any future study, in particular around how and when PWH may want to receive such information.

7.6.3 Evaluating clinical outcomes

Evaluating the clinical efficacy of the intervention was not the primary outcome of this study, although an exploratory analysis on outcome measure findings was included.

The group results from the outcome measures showed no clear improvements in the domains of pain, quality of life and function. Individual scores did show participants with scores achieving a meaningful clinical difference; however they were small. In isolation, such findings may appear to show limited value to the individuals taking part, but the post intervention interviews highlight an overall enjoyment with taking part as well as small individual improvements that were noted by participants.

Authors have highlighted the need for outcome measures that go beyond just annualised bleed rate and better reflect the improvements in medical care for PWH (386). A recent publication presented the outcome of a consensus approach to the development a core set of measures to be used in both research and clinical settings in haemophilia (387). The proposed set included the recording of number and location of bleeding events, health related quality of life, treatment adherence and joint health. Similarly, the development of the stakeholder informed PROBE tool sought to identify population level outcomes of importance for those with inherited bleeding disorders (113). Whilst assessments of pain and functional impairment were included here, it remains that such approaches continue to view the use of outcome measures in PWH along the lines of longer-term biomedical care provision (such as access to and success of, clotting factor concentrates). Their usefulness and acceptability for specific interventions such as physiotherapy remains unclear.

Whilst the participants in this study were accepting of the need to collect measures, they were less accepting of the applicability of the included outcome measures to them, even though these measures were chosen based on findings from the development work in chapters 3-5. It is plausible that such perceptions of identity may explain in part the lower response rate to return the outcome measures at 12 week follow up. The qualitative findings of this feasibility study emphasise a potential gap in attempts to bridge research and clinical necessities whilst trying to be truly person-centred. Further feasibility work is required to establish an acceptable method of measuring change with this intervention.

7.7 Reflexivity

Being actively reflexive within qualitative research requires complimentary approaches of reflection and interpretation. Reflecting on the individuals place in a research and clinical community and the traditions and expectations that accompany them, and then interpreting how this may influence the values, assumptions and language used (388). Such scrutiny helps enlighten the assumptions and dynamics of the research encounter, as well as the social embeddedness of the research (389). I have previously presented my position as clinician and researcher in Chapter 4, but I will provide some further discussion here in relation to the mixed methods approach used in this study.

The researcher was known to some participants at one of the study sites having worked there previously as the physiotherapist. Whilst the intervention was conducted by a different physiotherapist, it was I who performed the post-intervention interviews. Occupying the space between clinical activity, academic inquiry and professional identity is acknowledged as a potentially precarious position (390). However, recognising the potential benefits of this clinical-academic space whilst engaging in an actively reflexive approach, brings benefits to patients and care teams as well as the clinicians themselves (391, 392).

In comparison to the interviews and focus groups in chapter 4, I felt more relaxed and confident with my skills and ability in doing the interviews at this stage of my research process. I was very aware that participants may have felt the need to be overly positive about having taken part, given they knew that it was 'my project'. However, at the start of of the interviews I made it clear that I was open and very willing to hear about all of their experiences, positive and negative. Reflexivity was practised throughout, again using a reflexive journal to reflect on my initial thoughts after the interviews, as well as engaging in regular discussions with the wider research team. This all helped inform the process of codes and early themes development from the reflexive thematic analysis approach used, and in further evaluating this within the mixed methods analysis and presentation of the datasets. The participant responses in the interviews did reflect both positive and negative experiences, demonstrating a low risk of bias in the interviews and providing a rich source of contextual information to inform the analysis approach.

7.8 Trustworthiness

The criteria used to evaluate trust in qualitative research findings has been described previously in Chapter 4. Briefly, Lincoln and Guba (1985) state that the trustworthiness of qualitative research should be judged by the credibility, transferability, dependability and confirmability of the reported findings, alongside a clearly described reflexive process used by the researcher undertaking the research (304). As with the qualitative study in Chapter 4, the qualitative study included in the mixed methods approach in this chapter followed the phases described by Braun and Clark (273). Prolonged engagement with the datasets was key to the recursive approach used for data analysis and themes development. A particular strength of the mixed methods approach here was the ability to triangulate the qualitative data with the quantitative results from the feasibility study. Integrating the datasets in this way, and tabulating them, provides further credibility and dependability of the results presented. In detailing the process of evaluating both the quantitative and qualitative approaches within their respective philosophical domains and then describing how and why they were integrated, also established the dependability of the data used. The reflexive process described above, my position and reflections on my behaviours and thoughts whilst carrying out the study, helps further establish the transparency of the process used and trust in the findings presented.

7.9 Strengths

The main strengths of this study were the application of mixed methods in the data collection and analysis, the inclusive approach to recruitment and the pragmatic protocol design to encourage and facilitate participation in the study activities.

The advantages of using mixed methods in considering multiple viewpoints and positions to achieve a deeper understanding of the study findings (203) has been discussed previously in Chapter 2. Interviews with the participants and physiotherapists provided much needed insight as to the acceptance and potential benefit of a rehabilitative approach such as this particularly the issue of how best to evaluate outcomes. The interviews were also conducted by the researcher who had no role in the delivery of the study at each site. This distance helped establish a position whereby participants could be truthful about their experiences. Understanding the

experience of all who took part, as well more practical issues concerning burden of delivery and administration, means this study adds to the current quantitatively heavy evidence base of physiotherapy rehabilitation in haemophilia.

The inclusion criteria were purposefully broad. This acknowledges the highly complex nature of PWH living with multiple joint arthropathy and chronic pain, and reflects the real-world clinical experience. This corresponds to the MRC guidance in developing complex interventions described in chapter 2, where the study acknowledged the complexity and worked with it rather than against, such as participants being able to have their exercises modified to their own abilities. It is important when working with those living with rare disease, that study design does not further marginalise those who may have to most to gain from taking part. This is especially important for PWH as it remains unclear if established rehabilitation programmes addressing predominantly single joint issues such as Escape-Pain (393) and the GLA:D (296) would be suitable.

Even though this was a small feasibility study, two study sites were used. This meant the study was able to include two different groups of PWH under the care of different specialist physiotherapists. This was an important consideration for feasibility. If there were difficulties delivering this study at a local level within well-staffed haemophilia centres, then it is highly likely that it would not be at all feasible in centres with less than full time physiotherapy input. Two separate sites also gave further insight into the actual burden of delivering a study such as this in a single clinician service, such as that seen in haemophilia physiotherapy.

This is the first study of its kind in haemophilia to demonstrate the successful use of technology to deliver rehabilitation for people living with chronic pain. Being able to understand the benefits of this approach may future proof care delivery and be a way of providing specialist rehabilitation at a time and place more acceptable to the individual (394).

7.10 Limitations

There are acknowledged limitations with this study. Participant numbers were small so no statistical inference can be taken or implied from the findings described here. However, the study evaluation is in keeping with a feasibility design whereby the aim

was to elucidate if this study could be done in the way it was described, should it proceed and how (342). Given the small numbers of people affected by a rare disease such as haemophilia, effective feasibility evaluation is imperative to develop interventions that will be safe and effective.

Poor adherence to the return of the PROM questionnaires at the end of the intervention highlights a limitation of full evaluation of efficacy across the participant group. The questionnaires were posted with a prepaid, addressed envelope for return to their physiotherapist. The study protocol did not include instructions to the physiotherapists to follow up with participants after posting to encourage completion and return. Furthermore, even fewer postal returns of the PROM questionnaires at 3-month follow up was observed. Further work is required to ascertain when and how to best gather PROM data, their perceived value by participants, as well as consideration and evaluation of other methods of data return such as digital/electronic forms.

Whilst almost all participants had more than three joints affected by haemophilic arthropathy, the whole-body approach to the exercise programme was not fully acceptable to all. Some of the participants reported a desire to have had more joint specific exercises to focus on the joint most problematic to them at that time. There is a need to balance the practicalities of a high degree of individualisation, alongside evaluating feasibility and applicability of an exercise programme in a population based representative cohort such as those here.

The researcher was known to some participants at one of the study sites having worked there previously as the physiotherapist. Whilst the intervention was conducted by a different physiotherapist, the researcher did the post-intervention interviews, and so there may a risk of bias. Reflexivity was practised by the researcher throughout, engaging in regular discussions with the wider research team about the codes and early themes developing from the reflexive thematic analysis approach. The participant responses in the interviews also reflect positive and negative experiences, further demonstrating a low risk of interviewer bias in the interviews. Occupying the space between clinical activity, academic inquiry and professional identity is acknowledged as a potentially precarious position (390). However, recognising the potential benefits of this clinical-academic space whilst engaging in an actively

reflexive approach, brings benefits to patients and care teams as well as the clinicians themselves (391, 392).

Fidelity in delivery of the intervention was impacted by some of the participants using the telephone and not the virtual platform webcam. For some it was not acceptable due to issues with organisation and time, others were not comfortable in being on camera, even if only with the physiotherapist. Telephone delivered physiotherapy falls under the umbrella definition of telerehabilitation, although in the most part it is for giving advice and assurance rather than a real-time, verbal exercise programme (183). Overall fidelity of the webcam delivery was high, but the use of the telephone, rated positively by the participants using it, raises further questions relating to digital literacy, patient choice and equity of care in further iterations of studies such as this.

No measure of physical performance was included in this study. The choice not to include such an assessment was informed by the theory of change process, whereby stakeholders focussed on facilitating participation in the study. There was a wide range of individual physical abilities in the participants due to their own haemophilic arthropathy joint profile. The post intervention interviews highlighted the potential complexity in identifying a single performance measure that could be applied across a group such as this with various levels of impairment, different range of affected joints and different experiences of change identified afterwards. Further feasibility evaluation will be required on the need for, and value of, objective performance measures in PWH with chronic pain and multiple haemophilic joints.

7.11 Conclusion

An exercise-based, telerehabilitation intervention for people with haemophilia and chronic arthritic joint pain is feasible and acceptable. Feasibility was linked to the convenience of virtual delivery for participants, a feeling of safety whilst taking part and delivered by a physiotherapist who knew the participants and understood their haemophilia. The burden of study administration for physiotherapists in centres with less than whole time equivalent provision, however, requires further feasibility evaluation. Acceptability was associated with the ease of the using the virtual platform and the content and approach of the exercises included. Positive outcomes related to

enjoyment and individual changes in day-to-day life but with minimal change noted in the outcome measures. The present study highlights that further work is needed to evaluate the choice of objective outcomes used, as well as the value of including a more subjective, person centric experience of taking part in studies such as these.

The next chapter will discuss these findings in relation to the thesis as a whole, drawing together the findings from the previous chapters to synthesise and provide an overall discussion and conclusion in relation to the thesis aims and objectives.

Chapter 8 - Discussion

The overall aim of this programme of study was to develop and test the feasibility of an exercise-based telerehabilitation intervention for people with severe haemophilia and chronic pain associated with haemophilic arthritis (The REMAP-Haemophilia study). Use of the MRC framework for development of complex interventions (195, 196) helped inform and guide the process, and provide transparency in decision making and choice of methods used.

This chapter presents the overall discussion and conclusion for this thesis as a whole. It draws together the findings from the previous chapters: the background literature review (Chapter 1), systematic review of physiotherapy interventions for pain management (Chapter 3), qualitative study with PWH and healthcare professionals (Chapter 4), the stakeholder development of the programme theory to underpin the study protocol (Chapter 5) and the feasibility study including the nested qualitative study (Chapter 6 and 7). The findings are discussed in relation to the overall aims and objectives of the thesis and highlights the future research needs in this area.

8.1 Summary of main findings

The findings of the multi-centre feasibility study presented in this thesis provide evidence that an exercise-based telerehabilitation intervention is feasible and acceptable to PWH living with chronic pain and for the specialist physiotherapists that deliver it. However, limitations on acceptability of the outcome measures used, adherence to return of follow-up outcome measures and type of exercise activity for some participants mean that some uncertainty remains on feasibility design. Fidelity issues relating to delivery of the study may also require further development work with stakeholders to address the acceptability of a range of telehealth delivery options that are not just confined to the use of a webcam. Further feasibility evaluation may therefore be required to address these factors before embarking on further larger studies.

8.2 The current clinical and research landscape for pain management in haemophilia

Whilst modern therapies for managing haemostasis in PWH are highly effective, it remains that for many who grew up in an era with little or no treatment, musculoskeletal co-morbidities secondary to haemophilic arthropathy and associated pain remain a pressing clinical and personal issue. Acknowledging the historical context of medical care in haemophilia helps situate the medical advice that PWH were previously exposed to, as well as the coping strategies they developed as a way to manage bleeding, joint disease, and pain. In reviewing the literature relating to pain and pain management in haemophilia (Chapter 1), a predominantly biomedical approach of escalating pain medications was that most commonly described, with a focus on the pain and not the person living with the pain.

It has only been in recent years that a multi-disciplinary approach to pain management for PWH has been proposed. Although there remains a lack of evidence in how such an approach should be applied in this population. More specifically, a wide range of physiotherapy interventions have been proposed as potentially providing effective pain management. There remains however, a somewhat positivist focus on the need to evaluate a specific physiotherapy technique rather than an acknowledgement of the multi-dimensional nature of pain. This is to the detriment of being able to theorise how and why an intervention may, or may not, be having an effect.

Whilst there is an acknowledged need to improve management for pain in PWH, the view of pain as a multi-dimensional experience remains limited in the current literature in haemophilia. Consensus opinion from healthcare professionals remains focussed on pain medications as a first line approach in both acute and chronic pain (395), even though there remain deficiencies in how acute and chronic pain are defined and evaluated in studies with PWH (396). The narrative voice of the PWH is also notably lacking in such consensus opinion, and is particularly relevant given the findings of a recent UK study that indicated over 50% of PWH did not take pain medications even when they had joint pain (397).

Physiotherapists are increasingly recognised are key members of the healthcare team in helping people manage chronic pain (170), but their roles in the process are narrow and often unimodal (129). Physiotherapy interventions remain framed in a biomedical paradigm, with exercise for haemophilic arthropathy more associated with biomechanical concepts of joint stabilisation (102) than focussing on self-efficacy and daily functioning. The potential value of exercise based approaches is being recognised for use in those with chronic pain, but evidence of efficacy or potential mode of effect is currently very limited (103). This programme of study therefore aimed to address some of the key gaps that existed around the potential use of an exercise based rehabilitation approach for pain management in people with severe haemophilia and develop an intervention to test in a feasibility study.

A systematic review was conducted to explore the current evidence-base for physiotherapy interventions for pain management in PWH, focussing on identifying the specific interventions being investigated and the evidence of their effectiveness on measures of pain, functional activity, and quality of life (Chapter 3). Using a robust methodological approach, a well described extensive search strategy identified nine studies that matched the inclusion criteria. Due to insufficient clinical homogeneity in the included studies a meta-analysis was not indicated. The analysis highlighted a wide range of physiotherapy techniques applied to a range of different anatomical regions, across a broad age group of people with differing severities of haemophilia. The narrative synthesis found that there was low to very low quality of evidence of effect on pain intensity for the physiotherapy interventions described in the studies. Although hydrotherapy and land-based exercise appeared to have some positive effect on knee pain in PWH, the reporting quality was generally poor with a high risk of bias in the study. Interestingly, whilst all studies evaluated pain, none of them identified it as a specific inclusion criteria, and very few studies included evaluation of function or quality of life in their chosen outcome measures.

8.3 Exploring and understanding beliefs around pain and its management

The literature relating to pain management in PWH remains quantitatively biased, with most current guidelines recommending interventions that have limited or minimal

evidence of effectiveness. There is little contextual understanding of the views and beliefs of PWH on what their pain and its management mean to them, or how they would view the use of exercise as an option. The qualitative inquiry presented in Chapter 4 aimed to explore and understand these views and experiences. Fourteen PWH and six healthcare professionals participated in focus groups and individual semi-structured interviews. The use of a reflexive thematic analysis approach in data analysis provided a rich and complex understanding of the views of the participants. Pain was as much part of identify as living with haemophilia was, particularly as its presence had been there in some guise for most of their lifetimes. This lifetime experience meant that whilst there was some degree of acceptance of pain, there was a strong desire to be supported and shown ways of being able to better self-manage that pain with a strong emphasis on day-to-day function. Also, there was an awareness of the need to try and be more active to combat other health concerns associated with getting older. Ongoing management that included more pain medications was not acceptable. Exercise was broadly acceptable as option to try as a pain management approach, even if this meant that participating could be painful or result in some further pain. However, this was caveated with exercises needing to be personalised to their own physical ability, and the need to be able to trust in the knowledge and experience of the physiotherapist delivering such an approach.

Many of the findings in this study help to contextualise findings from other qualitative studies and builds a more coherent understanding of the many complex issues at play in relation to pain and its management. Similar to the findings in this study, the implications of chronic pain on identity and perceived physical ability have been reported by Canadian researchers. They also highlighted the particularly negative effects of pain and limited mobility on mental health and the need to try and normalise what was happening in order to fit in (398). PWH living with multi-joint lower limb arthropathy have described the anxiety of falling and pain as a major limitation to activity (123) and the importance of planning ahead to try and account for all eventualities, (286) similar again to findings here.

People with haemophilia are open to advice on what they can do to help themselves and want to be supported to do so (190). Exercise appears to be acceptable as a

concept to try for pain management but needs to be delivered by someone who understands the disorder of haemophilia, a theme similarly reported by Aliaga-Castillo and colleagues (348). The relationship between bleeding and pain is complex and the behaviours elicited are often initially focussed on the consideration for administering further clotting factor treatment. Many of the PWH in this study discussed the positive changes of newer haemostatic therapies on their experiences of bleeding, whilst acknowledging the other ongoing physical issues. This is similar to findings of a qualitative study investigating experiences of changing to a new non-factor based treatment which noted long standing joint damage, pain and limited access to physiotherapy was still preventing people from realising their full functional potential (399). However, other studies have shown positive effect on pain intensity in the short term (3 months) after switching to extended half-life factor concentrates for people with haemophilia B, but not for haemophilia A (400), highlighting again the complexity of the pain experience for PWH and the limitations of current knowledge.

Living with pain is a constantly evolving process for PWH, with their lived experiences helping inform decisions about their behavioural activities. It is imperative that such experiences are appreciated and understood in context and used to help inform better clinical practices towards pain management in PWH. This study highlighted that whilst the care of an experienced physiotherapist was highly valued, current physiotherapy interventions appear limited in addressing the lived experiences of pain. This means that such interventions are not adequately able to identify or influence outcomes that matter to PWH taking part.

8.4 Developing theory

The development of theory is identified as a core element of the MRC's complex intervention development framework (196). It is more than acceptable for the process of theory development to been done only using the findings of the literature, systematic reviews and the qualitative study described previously. However, the involvement of key stakeholders in theory development also helps strengthen the usability and applicability of the theory by situating its use in real world experience. Chapter 4 presented how a theory of change approach to theory development was used to define the contextual and causal outcome chains to be included in the

theoretical model. The stakeholders, three PWH and two haemophilia specialist physiotherapists, defined the overall outcome of an exercise-based intervention to be 'Living better with pain'. Whilst the group acknowledged that the aim of the current study would be to evaluate feasibility and not efficacy, there was clarity in the processes to be designed, included, and tested in the content and delivery of the intervention. They highlighted issues that would need to be addressed when trying to engage participants to take part, such as the times of exercise sessions being matched to haemophilia treatment days, as well as different session times to allow people of working age to take part. The group were cognisant of the need to design a meaningful intervention that would be as inclusive as possible for PWH, particularly those living with multi-joint haemophilic arthropathy. It was this that identified the low impact, moderate intensity approach used here and the need to incorporate different difficulty/effort levels of exercise so as to enable as many as possible to take part. The causal outcomes chains that would need to be in place at each stage of the process were also identified and linked to activities to be included to enable progression.

Theory aims to describe in detail how an intervention is proposed to have its effect and on what level. The use of this approach to theory development has not, to the researcher's knowledge, been described before in any intervention study in haemophilia. Including stakeholders in the theory development and intervention modelling as outlined in Chapter 4 provides a further point of triangulation between all the sources inputting into the theory development process, thereby strengthening the relevance and applicability of the output (194, 195).

In recent years, other rehabilitation-based interventions have included details of their theoretical underpinning and how it was developed. An intervention mapping approach was used to develop a study to support self-management of osteoarthritis and low back pain (SOLAS) (401). Initial interviews with staff and patients helped identify their needs relating to the intervention, with findings mapped against behavioural theory components. This was, however, the only step where the views of patient stakeholders were included. The remaining steps of the process focussed on the staff stakeholders who would deliver the intervention. The outcome was a well

described, transparent theoretical framework of behaviour change that aimed to influence self-management strategies.

A similar approach using intervention mapping was used for group education and exercise programme to promote self-management in low back pain, the GLA:D Back programme (402). A major difference here though was that the initial programme development involved only researchers and expert clinicians, with patient feedback only being sought after the initial pilot study was completed. In contrast, the recently published 'GREAT strides' study investigating gait rehabilitation for foot and ankle impairments in early rheumatoid arthritis had input from the patient stakeholders from the start (403). Although details of the programme theory itself was not published, the development process for the intervention included a series of patient/stakeholder workshops that informed the content and delivery of the intervention that was then successfully evaluated in a feasibility study. Given the novelty of this intervention within a rare disease cohort, the level of stakeholder involvement here was wholly appropriate and significantly strengthened the design of the resultant study. The clear explication of theory away from a positivist hypothesis testing, is in keeping with the critical realist position taken for the thesis as a whole.

The inclusion and explicit description of behaviour change theory, as well as identification of related behaviour change techniques, has not been well described in previous studies in PWH. Study protocol components of previous studies do appear to include activities that could be considered behaviour change techniques although they are not described as such. They mostly include use of patient diaries or training plans (BCT Self-monitoring of behaviour) (141, 231, 252, 404-406) and participant education sessions (BCT Information about health consequences) (232, 242, 248, 404-406). The vast majority of studies are delivered by physiotherapists with experience in the management of haemophilia (BCT Credible source). A common observation in all these studies is the lack of reasoning as to the inclusion of these components as well as the difficulty in determining the success (or not) of their inclusion in the subsequent results. One recent study investigated the use of shared medical appointments to change eating habits and physical activity levels lifestyles of PWH with obesity (407). They did specify seven BCT's included in the study intervention; goal setting, social

support, pros and cons, problem solving, monitoring of behaviour, information about health consequences and, social and environmental consequences. There was however no indication of how and why they chose these particular techniques, nor was their inclusion evaluated for efficacy in their analysis.

The advantage of the theory of change approach used here is that it can accommodate other theories within the structure or concept of the process map that is produced. The Behaviour Change Wheel was identified as an appropriate behavioural change theory to be used to support the development of the exercise intervention. After identifying the behaviour this study sought to change, that is, participating in this exercise study, the findings of the previous chapters alongside the theory of change map were then used to identify behaviour change techniques to be included. It is the inclusion and explication of this level of detail that will allow an explanation and evaluation of the 'how and why' and not just the 'what and when' of the planned feasibility study.

8.5 Evaluating feasibility and acceptability of the REMAP-Haemophilia study

The methods for the REMAP-Haemophilia feasibility study were described in Chapter 6 and the results of the study were presented in Chapter 7. The study was delivered virtually using the MS Teams platform. Ten participants with severe haemophilia and chronic pain were recruited across two different sites. They took part in a 12 session, low impact-moderate intensity exercise programme delivered by their own specialist haemophilia physiotherapist. The study included a nested qualitative study at the end of the programme, whereby participants and the physiotherapists were interviewed about their experiences of taking part. The main objective of using quantitative and qualitative approaches to evaluate the indicators of feasibility and acceptability were met. These were analysed independently before then being integrated to provide a complementary, in-depth analysis of the study findings. The overall results confirmed that the REMAP-Haemophilia study was feasible and acceptable to both PWH taking part and the physiotherapists delivering it.

Limitations of feasibility were identified. They included the time needed to deliver the study by the physiotherapists, difficulty with some exercises because of ankle arthropathy and postal return of follow up outcome measures. The intervention was broadly acceptable, with high levels of enjoyment and behaviour change reported, although the choice of outcome measures were not fully acceptable to those taking part. The inclusion of the qualitative interviews provided insight into improvements and positive changes experienced by participants that the quantitative measures did not capture. This included the decreased burden on daily routine of having a virtual exercise programme and the value of taking part in a programme designed with the physical abilities of PWH in mind.

The REMAP-Haemophilia feasibility study was novel in its design and delivery. The lack of good quality rehabilitation studies in PWH, particularly in relation to those with chronic pain highlighted the need for a well described, stakeholder informed, theory-based intervention that could be tested in a feasibility study. This approach is much needed to improve the quality of trials investigating rehabilitation interventions in general (340), minimising research waste (408) and improving the potential for further meaningful iteration of interventions. They may be particularly useful in research within rare disorders to improve methodology and delivery, thereby enhancing the design of larger trials (409).

The exercise intervention itself was described in detail in keeping with the Consensus in Exercise Reporting Template (CERT) (410). This included who delivered it, how it was delivered, where and when, the dosage and intensity, the degree of tailoring within exercises and if it was delivered as planned. Such transparency in detail permits replication as well as evaluation of potential mechanisms of efficacy within the study's underpinning theory. The exercises were chosen based on the input of the stakeholders, with a particular importance placed on inclusivity for as many physical abilities as possible. A mix of cardiovascular and resistance exercises targeted a whole-body approach, carried out at moderate intensity, and was acceptable to all participants, although some did also want more joint specific exercises.

The benefits of exercise for general health and well-being are well established, and more exercise prescription has been encouraged for PWH (411). Whilst this study confirms the feasibility, acceptability, and safety of using exercise, there remains conflict in the recommendations for giving exercise to PWH with pain. A widely referenced paper recommends that exercises in PWH should be carried out pain free (412), which is all but impossible for many PWH living with chronic pain associated with their haemophilic arthropathy. However, being able to exercise with pain may likely bring benefits. Doing so however, requires a reconceptualization of pain away from a purely biomechanistic view towards one that demonstrates safety even in the presence of pain and supporting people to find ways to mitigate and moderate that pain (413).

The exercise approach used here appears to have had a positive effect on motivation to be more active in daily life, and to moderate the disruptive effect of pain interference in activities. There was joy in the discovery of their own abilities to participate, as well as general enjoyment of doing the exercises as well, particularly for those who took part in the group sessions. A recent qualitative study explored the perspectives and self-management behaviours of people living with multiple health conditions that included arthritis (338). They highlighted the benefit of the social dimension of exercise and achieving an improved sense of belonging and relatedness through exercising with others. The exercise approach here was informed by the stakeholders and designed to be as inclusive as possible. It is this insight to identity in a disorder and life with joint impairment that strengthened the acceptability. The enjoyment of the programme was attributed, at a basic level, to being able to do the exercises even with their level of joint disease, the repetition, being able practice the technique, and feeling themselves improve as the weeks went on. Enjoyment in doing exercises has been shown to be a positive mediator of activity levels (414), and so it is concept that needs to be considered, and measured, when designing and implementing study protocols.

The identification and inclusion of behaviour change techniques in the study design strengthened the feasibility and acceptability. Qualitative analysis of the post

intervention interviews highlighted five common BCTs associated with the experience of participating. They were action planning, credible source, information about health consequences, self-monitoring of behaviour and goal setting (behaviour). A recent systematic review of BCTs used in studies targeting persistent musculoskeletal pain reported moderate effect for social support, goal setting, instruction of behaviour, demonstrating behaviour and behavioural practice/rehearsal (415). The authors suggested that studies should aim to include less rather than more BCTs. This was in contrast to another review by Eisele and colleagues that suggested more BCTs was better than less (416). In their review of using physical activity for chronic musculoskeletal conditions, they concluded that studies with more than 8 BCT's showed slightly better effect adherence to activity. The approach used in the REMAP-Haemophilia study included 21 BCTs in the overall design of the study, as well as within specific activities that would be directed to participants. The primary aim of this study was to establish feasibility and acceptability, so no recommendations can be inferred towards short or medium-term efficacy of the BCTs on participant behaviours. However, the design of the study to engage people to participate and be able to do the exercise activities was successful. Further studies are required to fully evaluate the potential value of including behaviour change theory in studies such as this with PWH, with care taken to fully describe such interventions so that studies can be evaluated against each other (322, 334).

Preliminary findings of efficacy from the outcome measures highlight a potential limitation of quantitative measurement tools that may not fully encompass individual views of their haemophilia and pain experiences. The participant interviews highlighted their participation as being a wholly positive experience, with enjoyment of the exercises and routine an important aspect helping realise positive changes in day-to-day activity, even with pain. This experience based, iterative feedback loop is what forms the basis of the mature organism model to explain pain, proposed by Gifford (97). In it, pain is conceptualised as multi-dimensional, individually constructed experience that is continually being scrutinised, evaluated, and assimilated based on the experiences in external and internal environments. Ongoing behaviours are then modified according to these positive or negative experiences. This study and its

activities within, represent another life experience for those participants with haemophilia living with pain. It reflects the theme findings in Chapter 4, and provides a positive outcome to be scrutinised against their previous experiences of pain and exercise, potentially influencing their future behaviours. The stakeholder informed study design acknowledges the existence and importance of context for those taking part, and when taken alongside the inclusion of the BCTs, it provides a potential explanation for the 'black box' of this intervention.

8.6 Strengths and limitations

Strengths and limitations for each component of the study have previously been reported in the relevant discussion chapters. Those presented below are additional factors that need to be considered when reviewing the thesis as a whole.

8.6.1 Strengths

The main strength of the overall design for the study was using the MRC framework to guide and inform the development and feasibility testing of the intervention (195, 196). The detailed approach in reporting the development process used here reflects the recommendations by Bleijenberg and colleagues (194), and provides transparency in that process. Furthermore, the detailed reporting of the theory development, the process of identifying behaviour change techniques and robust description of the exercise intervention, in keeping with the consensus in exercise reporting template (CERT) (155), strengthens the validity of the entire process and allows other researchers to fully evaluate the quality and reproducibility of the resultant intervention.

Another key strength was the use of a mixed methods research approach in the design of the feasibility study. As detailed in Chapter 2, the collection and integration of both qualitative and quantitative data enables a broader and a deeper analytic picture of the findings in the REMAP-Haemophilia feasibility study (203). Reliance solely on quantitative techniques to evaluate measures of feasibility and acceptability would have provided sufficient information on recruitment, retention and adherence but would have been insufficient in the preliminary evaluation of efficacy, given the minimal differences recorded in the outcome measures. The inclusion of a nested

qualitative evaluation in the study design meant that data relating to enjoyment, experiences and changes in daily life as result of taking part actually strengthened many facets of acceptability of the intervention. It also highlighted the potential limitations of the chosen outcome measures as described by the participants, therefore informing the need for further evaluation of this aspect of study design.

Involvement of stakeholders is identified as a core element in the development of complex interventions (196) and this programme of study was informed, supported and improved by the input and partnership from stakeholders throughout. In the pre-development phase for this thesis, the researcher engaged at length with the Haemophilia Society and people with haemophilia in his clinical environment. Formalised stakeholder involvement in this programme of study was in two parts. The first was to invite a PWH to be a key member of the research management group. This appointment brought balance to the group and enabled open discussions about intervention design processes and the concept of need and delivery within NHS sites, and other aspects such as language being used in participant facing documents improved that which was produced. The second was the inclusion of PWH stakeholders in the theory of change development process. This has never before been reported in studies in haemophilia, however this process added significant value to the quality and applicability of what was produced. Whilst it is accepted that three people may be considered small or potentially biased, the results of the feasibility study would imply that this process has benefit. The persistent focus on a gold standard approach to co-production is seen as divisive. Smith and colleagues view co-production as an exploratory social space and generative process, and recommend instead that researchers should be happy to give it a go and try a diversity of approaches. Researchers should be content with pragmatic decisions that are tailor made to their specific contexts and people, and acknowledge where compromise was done and why (417). Given the time and financial constraints associated with this PhD programme, the extent of stakeholder involvement and the approaches used were considered appropriate and successful in creating an intervention that was meaningful and acceptable to PWH.

A further strength of the REMAP-Haemophilia study was the advanced registration of the study protocol on the internationally recognised ISRCTN registry (Identification number – 17454597). Doing so facilitates a transparency in the research being undertaken and decreases the risk in selective reporting of results (418, 419). This is particularly important in rare diseases such as haemophilia where studies are likely to have smaller numbers of potential participants anyway, but it is also a question of trustworthiness in any data that may be made public, helping inform others of the governance and approach of the study undertaken (420).

8.6.2 Limitations

The small sample size of participants recruited, and lack of control group may be considered a limitation, particularly as no recommendations can be made on statistical inference of effect or estimations of sample size for further larger trials. However, the primary aim of this study was feasibility and acceptability, that is, could this study be done in the way it was described, and should it proceed to further evaluation. Therefore, it did not include a formalised hypothesis of efficacy. Feasibility studies have been shown to be inadequate in predicting future sample size (344) and there remains uncertainty in the literature as to how many participants are enough (421). Sample size should however always be justified even when sample size is not appropriate to be calculated (422).

Many aspects of the REMAP-Haemophilia study were novel. The added issue of haemophilia as a rare disease and current limits on physiotherapy provision for PWH, meant a focus on a feasibility of delivery and acceptability was appropriate, thus justifying the sample included. Further studies will be able to review and evaluate the current study, facilitating ongoing iterative development and informing future appropriate statistical approaches.

Due to constraints of time and financial limitations associated with the study design and delivery, the lead researcher undertook all participant interviews and focus groups. There is, therefore, an acknowledged potential risk of bias in how participants may have chosen to respond to questions by being more positive in their feedback or less truthful, especially as some of the participants were also know to the researcher

from his clinical workplace. The researcher was also responsible for the thematic analysis of the transcripts from those interviews and focus groups, introducing potentially further bias in data analysis and conceptualisation of themes. The researcher's 'insider' position as an experienced clinician bridging into the academic field has been identified as creating both challenges and benefits to the research process. Being a researcher familiar with both the professional work and the clinical environment requires a careful navigation of the middle ground of insider/outsider (390). In the acknowledgement of that position, the researcher has to draw on aspects of themselves to negotiate a respectful positioning in the group, whilst ensuring to keep an analytic degree of distance (390, 392). Reflexivity was maintained throughout the analytic process. This was facilitated by regular supervision with the wider research team and ongoing discussions of assumptions made from the qualitative inquiry, and the developing narrative being produced from that analysis.

Due to the feasibility design, no recommendations can be made on efficacy of the intervention tested in the REMAP-Haemophilia study. The lack of a control group and no blinding of participants are methodological limits that mean the positive changes in quantitative results may be due to a biased estimate of effect. The use of a mixed methods research approach in the study does, however, provide additional context to the results within the experiences of those taking part. The overall success of the feasibility and acceptability objectives, as well as the enjoyment reported by those taking part suggests that this approach remains worthy of further evaluation for overall efficacy.

There was a lack of a clear outcome measure that was fully acceptable to those that took part in the study, thereby limiting the ability to determine quantitative success of the intervention as it currently stands. The choice of outcome measures included in the study was informed by the findings of the qualitative study in chapter 4, as well as the theory development and process modelling for the intervention itself. This issue perhaps highlights the complexity in trying to measure success and by whose standard, especially given the positive feedback from participants taking part in the REMAP-Haemophilia study. Although the measures aimed to evaluate different but complimentary domains of pain, quality of life and function, it is possible that there

may have been too many included. Complex interventions with too many components may in fact provide less information on the evaluation of the potential effect (306), but being able to work such issues out at a feasibility stage helps clarify such components for future studies.

The generalisability of the results of this programme of work needs to be considered. Whilst attempts were made to engage with as diverse a cohort of PWH as possible, it must be noted that all those who participated in the interviews/focus groups have regular access to an expert haemophilia physiotherapist. Their experiences of pain management, exercise and previous exposure to similar self-management approaches may be different to those PWH registered in centres with limited or no physiotherapy expertise. Similarly, the feasibility study was conducted in two haemophilia centres with full time haemophilia physiotherapy provision. Therefore, the feasibility of this intervention approach in centres with part time haemophilia physiotherapy input will require further feasibility evaluation. However, it was first important to establish the feasibility of the REMAP-Haemophilia study in centres with sufficient physiotherapy, as had it not worked in those centres then it is highly questionable if it could be done in less resourced environments.

Little is known about the effect of pain on rehabilitation strategies for people living with multi-joint arthropathy and if particular combinations of joint disease positively or negatively influence outcome of intervention. The location and severity of joints affected with haemophilic arthropathy also needs to be considered for generalisability of findings. Only 1 of the 10 PWH included in this study had two joints affected by arthropathy, with 8 people having 4 or more joints affected. All were on a high standard of haemophilia prophylaxis treatment. Findings of the post-intervention interviews suggested that the presence of ankle arthropathy was a limit to being able to do some of the exercises. In countries with limited or minimal access to adequate haemophilia treatment, willingness of PWH to do this type of intervention may be different or impaired depending on their beliefs and anxieties about activities and potential bleeding.

8.7 Clinical implications

The REMAP-Haemophilia study was designed for delivery by specialist haemophilia physiotherapists using an online communication platform. The development phase of this body of work synthesised findings from the systematic review, qualitative study, and the theory development workshop to inform the overall study protocol. These earlier studies, however, did highlight findings that are worthy of consideration for current and future clinical practice.

The current evidence base for physiotherapy interventions highlights a predominating focus on biomechanically driven interventions. As well as low quality evidence of effectiveness, they do not appear to acknowledge or facilitate the need for self-efficacy or ongoing self-management approaches. Enabling self-efficacy to improve self-management in inflammatory and osteo-arthritises is a key inclusion in the European League Against Rheumatism (EULAR's) recent recommendations for pain management with this cohort (100). People with higher levels of perceived self-efficacy in conditions such as osteoarthritis and rheumatoid arthritis have been shown to cope better with their pain and be more active (423, 424). In PWH, lower self-efficacy was shown to be associated with lower activity levels, but was improved in those who received guidance and support on how to be safe with activity (425) . The importance of support for activity on self-efficacy levels has even been highlighted as a need in younger people with haemophilia with minimal joint damage (426). Clinicians need to be considerate of the interventions they are choosing to use for pain management with PWH in their care. The use of low-quality evidence interventions that do not appear to enable self-management in more health-promoting physical activities should be questioned, with other strategies explored that may be of more benefit on function and well-being.

The findings of the qualitative study highlighted concerns that PWH have with the current approaches to pain assessment when attending their clinical review appointments. The interviews and focus groups highlighted a disconnect about how pain is discussed with clinicians, as well as a low value perception of assessment approaches that required them to rate their pain on a 0-10 scale. People with haemophilia who have lived with pain for many years report that they would rather be

engaged in discussions about what they can do to help themselves as well as be supported to do so, with the option of further pain medications in particular rating very low on self-management approaches. Ongoing communication and a less medicalised approach appears to be something that PWH want to engage in to try and live better with the pain that they have. Haemophilia care teams should aim to facilitate conversations around how pain is for each individual and engage in developing person-specific strategies that they can try to do at home with adequate support.

The REMAP-Haemophilia study demonstrates that a relatively simple, low impact/moderate intensity exercise approach is safe and enjoyable for PWH who have painful haemophilic arthritis. The virtual delivery method was shown to be safe and highly acceptable to participants, with those in the study keen that it remained an option for day-to-day clinical practice. The focus on exercise for the whole body, with repetition and gentle progression showed unexpected benefit for some people. They noticed improvements in their general fitness and mental health and surprised themselves at what they were actually able to do and how much they enjoyed it. This study highlights the value of doing exercise even for people who feel they may not be able to, or that their pain prevents them from seeing the potential they may have to do something. Haemophilia healthcare teams are highly regarded and trusted by PWH, and this already established therapeutic relationship should be used as the catalyst to try and get people moving and exercising more, as the benefits appear to outweigh the risks of not trying at all.

8.8 Contributions to knowledge

This thesis has added to the knowledge base in a number of ways. The extensive literature review and synthesis of findings relating to the current approach to pain management in PWH highlight the significant gaps remaining in this aspect of care. Furthermore, the systematic review provides a detailed overview on the effects of a range of physiotherapy interventions for pain, quality of life and function as outcomes, adding to the findings of other similar reviews on exercise.

The findings of the qualitative study provide a novel understanding of early and ongoing life experiences of pain for PWH, and how such experiences influence decisions on movement, physical activity and perceptions of pain. Importantly this study is one of the first to provide an understanding of the beliefs and expectations of using exercise as a pain management strategy when living with chronic pain associated with haemophilic arthropathy.

This thesis presents the development and explication of the stakeholder informed theory underpinning the intervention. This is, to the researcher's knowledge, the first time such an approach has been described in any rehabilitation intervention for PWH. In doing so, it shows how shifting the power and philosophical dynamic of intervention development from a positivist clinician perspective to that of a stakeholder informed, brings value and meaning to the overall process.

The findings of the REMAP-Haemophilia add to the currently limited body of evidence around exercise-based approaches for pain management in PWH. The thesis presents how this low impact, moderate intensity exercise intervention, delivered in real-time using a virtual platform is safe, feasible, acceptable, and enjoyable to PWH. The mixed method approach employed in the study, integrating the quantitative and qualitative findings was a novel study design and added further to the applicability of the findings. To the researcher's knowledge this is the first time an approach such as this has been described in a cohort of PWH.

8.9 Recommendations for future research

The outcome measures included in the REMAP-Haemophilia study were chosen based on the development work prior to the study protocol development. Whilst they did cover aspects of pain, quality of life and function, the post-intervention interviews highlighted limitations in their acceptability. Only one measure, the Haemophilia Activities List questionnaire, was condition specific. A recent consensus agreement on the need for a core set of outcome measures in haemophilia identified 5 that were recommended for use in research and clinical contexts. They were total bleeding events, EQ5D5L, a measure of treatment adherence, joint health measured by the haemophilia joint health score (HJHS), and the number and location of bleeds (387). It

is clear however, that a focus on outcomes of disease/condition modification as opposed to outcomes relating to specific interventions for symptom management, means that the core set remains extremely limited for pain research in haemophilia. Further research is needed to identify how PWH would prefer pain and functional issues associated with it to be measured, by whom and in what situations. The potential value of qualitative narrative reports of the pain experience requires further evaluation, as this study highlighted differences in the outcome measure findings against reporting of their own individual experiences.

The feasibility design means that conclusions cannot be drawn on effectiveness of the intervention as a pain management strategy. Whilst the content and approach of the intervention were feasible and acceptable for the 6-week duration, it remains unclear what the most appropriate length and dosage of delivery may be for people with severe haemophilia and arthropathy. Other exercise based interventions for knee OA such as the GLA:D programme (296) and Escape-pain (393) similarly use a 12 session/6 weeks format. However, both programmes focus on the knee only, and use group exercise sessions with education components a key feature throughout. Further research is needed in trying to establish the optimum intervention length of a rehabilitation intervention for PWH with multiple affected joints, and how issues such as the presence of ankle arthropathy may inhibit or limit the potential effect on other joints.

As a result of the worldwide Covid-19 pandemic, there was a urgent shift to consider how healthcare could be provided. With the technology now readily available for healthcare professionals to use, the opportunities of telemedicine are promising. Whilst this study demonstrates the safety, feasibility, and acceptability of a wholly virtual approach in delivering this exercise intervention, many outstanding questions remain. This study sought to evaluate real time delivery via webcam, however in some instances participants were able to successfully participate using only the phone. Further studies should consider evaluating the efficacy and acceptability of different modes of telemedicine. This may provide a range of options for people with limited digital literacy or social opportunities wishing to access rehabilitation and those with limited or restrictions to access due to digital poverty.

Comprehensive haemophilia care is situated in a limited number of hospitals across the county, so many PWH do not live in close proximity to their treatment centre. Telerehabilitation offers the prospect of equity of access to people without the burden of time lost to travel. The REMAP-Haemophilia study was delivered in real-time, with the physiotherapist leading each session. Options for including downloadable audio files or videos of exercise sessions for people to use in their own time may provide further opportunities to facilitate self-efficacy and participation in activity in their own familiar environments. There is a need also to evaluate the opportunities that a blended approach of face to face and real time virtual rehabilitation sessions may bring to both clinicians and PWH.

Whilst haemophilia care is concentrated in a few centres, there are limitations in what physiotherapy access is available, as it remains that approximately 60% of PWH have limited or no access to regular physiotherapy (372). The REMAP-Haemophilia study highlights how expert haemophilia physiotherapy care can be delivered remotely. Researchers at policy and service provision level may want to consider the potential of a hyper-regional access to haemophilia physiotherapy offered using virtual technology. Such an approach would require extensive feasibility and acceptability evaluation, particularly relating to the importance of established therapeutic relationships that have been identified in this study.

An unexpected finding from this study was the subjectively reported improvements to mental well-being and sense of health and fitness improvements by participants. Each session required the participants to work towards a steady moderate intensity of between 4-6 on the RPE scale. Depending on their attendances at all sessions, most had between 30-70 mins of moderate intensity per week from taking part in the REMAP-Haemophilia study. Current guidance for physical activity for adults in the UK is for 150 mins of moderate intensity activity (427), which is substantially more than that incorporated into the study. Measurement of physical activity was not included in the baseline data, nor was it assessed throughout the study, other than one question about days of activity per week that was included in the MSK-HQ outcome measure. These initial small subjective changes in wellbeing may imply the positive effect of even small additional periods of physical activity. Future studies should consider the

value to general health as well as pain, of a more holistic view of physical activity that focusses on individual abilities and helping people to find a way to be active.

This PhD offers novel insights into the potential for exercise in pain management in PWH. It has generated new knowledge and a clear and transparent programme theory that underpins the approach used. It has added to the current understanding of the experiences of pain in PWH, added to the evidence base for non-medical approaches for pain management in PWH and has identified areas of future research need. The involvement of stakeholders with haemophilia in the research management group and in the development of the programme theory and intervention is described. In doing so it successfully highlights the immense value that is added by those with lived experience to the process of complex intervention development.

Next steps include an iterative review of the theory described in this thesis. This will be initiated with another theory of change workshop with the same stakeholders, where the group will be tasked with reviewing the results of the feasibility study against the current theory process map. The outcome of this process will then be used as the basis to inform further evaluation of outcome measure as well as to establish if a larger, randomised trial is an appropriate next step.

The acknowledged benefits of physical activity to the individual and wider society, and the significance of exercise as an option in managing long term musculoskeletal impairments, show how vital research in this aspect of haemophilia is. Given the rapidly evolving landscape of treatments for haemophilia that provide much improved haemostatic cover, as well as life expectancy, person-focused, evidenced based interventions for pain management are crucial in enabling people to live better with their pain. The implications on clinical practice and for PWH, of well designed, stakeholder informed, meaningful interventions for pain management and functional enablement are likely to be substantial.

Chapter 9 - Conclusion

The studies that comprise this thesis show that chronic pain associated with haemophilic arthropathy presents a significant burden to PWH, and with it, challenges to establishing effective management approaches for those in clinical practice. For many, pain exists in a coalition with their identity as a person with haemophilia. There is a desire to be supported in ways that allow PWH to try and live better with that pain, and be able to participate in meaningful daily activities. An approach that involved exercise was one that PWH agreed could be beneficial, but it would need to be tailored to their abilities and be delivered by someone who understood them and their haemophilia.

The REMAP-Haemophilia feasibility study confirmed that it is possible, acceptable and safe to deliver an exercise based telerehabilitation intervention for PWH who have chronic pain. The stakeholder informed, inclusive design of the intervention, particularly the low impact, moderate intensity approach used was successful in eliciting participation and benefit to all who took part. The use of a mixed methods approach was beneficial in highlighting the limitations with current outcome measures in evaluating perceived change and enjoyment as a result of taking part.

Further development work is needed in evaluating the choice of outcome measures used, the potential administration burden on clinicians undertaking this intervention, and whether or not PWH are interested in participating in group exercise sessions. The successful delivery of this intervention using a real time, virtual communication platform highlights the novelty of this study and the potential value for such approaches in future studies.

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Appendix A - Data extraction form for systematic review

Review title or ID	
Study ID *(surname of first author and year first full report of study was published e.g. Smith 2001)*	
Report ID	
Report ID of other reports of this study including errata or retractions	
Notes	

General Information

Date form completed *(dd/mm/yyyy)*	
Name/ID of person extracting data	
Reference citation	
Study author contact details	
Publication type *(e.g. full report, abstract, letter)*	
Notes:	

Study eligibility

Study Characteristics	Eligibility criteria *(Insert inclusion criteria for each characteristic as defined in the Protocol)*	Eligibility criteria met? Yes	No	Unclear	Location in text or source *(pg & ¶/fig/table/other)*
Type of study	Randomised Controlled Trial	☐	☐	☐	
	Quasi-randomised Controlled Trial	☐	☐	☐	
	Controlled Before and After Study Contemporaneous data collection Comparable control sites At least 2 x intervention and 2 x control clusters	☐	☐	☐	
	Interrupted Time Series At least 3 time points before and 3 after the intervention Clearly defined intervention point	☐	☐	☐	
	Other design (specify):	☐	☐	☐	
Participants		☐	☐	☐	
Types of intervention		☐	☐	☐	
Types of comparison		☐	☐	☐	
Types of outcome measures		☐	☐	☐	
INCLUDE ☐	EXCLUDE ☐				
Reason for exclusion					
Notes:					

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

Characteristics of included studies

Methods

	Descriptions as stated in report/paper		Location in text or source *(pg & ¶/fig/table/other)*
Aim of study *(e.g. efficacy, equivalence, pragmatic)*			
Design *(e.g. parallel, crossover, non-RCT)*			
Unit of allocation *(by individuals, cluster/ groups or body parts)*			
Start date			
End date			
Duration of participation *(from recruitment to last follow-up)*			
Ethical approval needed/ obtained for study	☐ Yes ☐ No ☐ Unclear		
Notes:			

Participants

	Description *Include comparative information for each intervention or comparison group if available*	Location in text or source *(pg & ¶/fig/table/other)*
Population description		
Setting		
Inclusion criteria		
Exclusion criteria		
Method of recruitment of participants *(e.g. phone, mail, clinic)*		
Informed consent obtained	☐ Yes ☐ No ☐ Unclear	
Total no. randomised *(or total pop. at start of study for NRCTs)*		
Clusters *(if applicable)*		
Baseline imbalances		
Withdrawals and exclusions		
Age		
Sex		
Race/Ethnicity		
Severity of illness		
Co-morbidities		
Other relevant sociodemographics		
Subgroups measure		
Subgroups reported		
Notes:		

Intervention groups

Copy and paste table for each intervention and comparison group

Intervention Group 1

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Group name		
No. randomised to group		
Theoretical basis *(include key references)*		
Description *(include sufficient detail for replication, e.g. content, dose, components)*		
Duration of treatment period		
Timing *(e.g. frequency, duration of each episode)*		
Delivery *(e.g. mechanism, medium, intensity, fidelity)*		
Providers *(e.g. no., profession, training, ethnicity etc. if relevant)*		
Co-interventions		
Economic information *(i.e. intervention cost, changes in other costs as result of intervention)*		
Resource requirements *(e.g. staff numbers, cold chain, equipment)*		
Integrity of delivery		
Compliance		
Notes:		

Outcomes

Copy and paste table for each outcome.

Outcome 1

	Description as stated in report/paper		Location in text or source *(pg & ¶/fig/table/other)*
Outcome name			
Time points measured *(specify whether from start or end of intervention)*			
Time points reported			
Outcome definition *(with diagnostic criteria if relevant)*			
Person measuring/ reporting			
Unit of measurement *(if relevant)*			
Scales: upper and lower limits *(indicate whether high or low score is good)*			
Is outcome/tool validated?	☐ Yes ☐ No ☐ Unclear		
Imputation of missing data *(e.g. assumptions made for ITT analysis)*			
Assumed risk estimate *(e.g. baseline or population risk noted in Background)*			
Power *(e.g. power & sample size calculation, level of power achieved)*			
Notes:			

Other

Study funding sources *(including role of funders)*		
Possible conflicts of interest *(for study authors)*		
Notes:		

Risk of Bias assessment

Domain	Risk of bias Low High Unclear	Support for judgement *(include direct quotes where available with explanatory comments)*	Location in text or source *(pg & ¶/fig/table/other)*
Random sequence generation *(selection bias)*	☐ ☐ ☐		
Allocation concealment *(selection bias)*	☐ ☐ ☐		
Blinding of participants and personnel *(performance bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Blinding of outcome assessment *(detection bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Incomplete outcome data *(attrition bias)*	☐ ☐ ☐	Outcome group: All/	
(if separate judgement by outcome(s) required)	☐ ☐ ☐	Outcome group:	
Selective outcome reporting? *(reporting bias)*	☐ ☐ ☐		
Other bias	☐ ☐ ☐		
Notes:			

Other information

	Description as stated in report/paper	Location in text or source *(pg & ¶/fig/table/other)*
Key conclusions of study authors		
References to other relevant studies		
Correspondence required for further study information *(from whom, what and when)*		
Notes:		

Appendix B - GRADE Criteria for Systematic Review

STUDY TITLE:			
GRADE criteria	**Rating (circle one)**	**Footnotes (reason for down- or upgrading**	**Quality of the evidence (circle one)**
OUTCOME: **Pain Intensity**			
Study design	RCT (starts a high quality) Non-RCT (starts as low quality)		**++++** **High** **+++0** **Moderate** **++00** **Low** **+000** **Very low**
Risk of Bias (Cochrane tables)	No Serious (-1) Very serious (-2)		
Inconsistency	No Serious (-1) Very serious (-2)		
Indirectness	No Serious (-1) Very serious (-2)		
Imprecision	No Serious (-1) Very serious (-2)		
Publication Bias	Undetected Strongly suspected		
Other (upgrading factors, circle all that apply)	Large effect (+1 or +2) Dose response (+1 or +2) No plausible confounding (+1 or +2)		

Appendix C - Systematic Review publication

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REVIEW ARTICLE
Musculoskeletal

Haemophilia WILEY

Physiotherapy interventions for pain management in haemophilia: A systematic review

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Abstract

Purpose: Approximately 35%-50% of people with haemophilia (PWH) report living with chronic musculoskeletal pain. Although exercise based rehabilitation is effective for pain in other arthritises, there are no published guidelines for management of chronic pain in PWH. This review aims to evaluate and appraise the current evidence of effectiveness of physiotherapy interventions on (a) pain intensity, (b) quality of life (QoL) and (c) function in PWH.

Methods: A systematic review of five databases AMED and CINAHL, EMBASE and MEDLINE and PEDro, as well as trial registries, grey literature and hand searching key journals was completed. Included studies were critically appraised and evaluated for risk of bias. The GRADE approach was used to rate the quality of the evidence.

Results: Nine trials consisting of 235 participants met the inclusion criteria. All studies had an overall risk of bias with low methodological quality. Meta-analysis was not possible due to heterogeneity across trials. Studies comparing a range of physiotherapy interventions against no intervention showed no clear beneficial effect on pain intensity or QoL. Only one study, investigating hydrotherapy or land-based exercise against control, showed positive effect for pain intensity, but rated very low on GRADE assessment. Studies comparing one physiotherapy intervention against another showed no clear benefit on pain intensity, QoL or function. LASER with exercise and hydrotherapy were shown to have some positive effects on pain intensity, but no clear benefit on function.

Conclusions: At present, there is limited evidence for the use of physiotherapy interventions in addressing the issue of pain in PWH. Better designed trials with higher quality and explicit methodology along with user involvement are needed to assess the efficacy of any proposed intervention.

KEYWORDS
arthropathy, Haemophilia, pain management, physiotherapy

1 | INTRODUCTION

Haemophilia is an inherited bleeding disorder characterized by recurrent and spontaneous bleeding into joints and muscles and fatal bleeding in the untreated state.[1,2] People with haemophilia (PWH) experience transient episodes of acute pain from an early age from musculoskeletal bleeding episodes. Despite replacement therapy, some PWH continue to have bleeding into their joints and muscles, which can lead to debilitating arthritis with chronic and recurrent pain.[3]

People with haemophilia over the age of 65 had no access to regular treatment until they were in adulthood, with those currently aged in their 40's having no access to effective treatment for the majority of their childhood.[4] Consequently, many PWH have chronically painful, multi-joint haemophilic arthritis, involving elbow, knee and ankle joints.[5-7]

Between 35% and 50% of PWH report living with chronic musculoskeletal pain,[7-10] with 40% reporting their pain is poorly managed by their healthcare provider.[8] PWH living with pain report limitations in mobility and independence, increased anxiety, poor quality of life and frustration due to restrictions in activities of daily living.[7,11,12]

A recent systematic review of management of multisite osteoarthritis (OA) found that exercise interventions may have moderate benefits on pain, function and quality of life.[13] More specifically, aerobic exercise has been shown to be effective for pain management and functional improvements in rheumatoid arthritis[14] and in OA when used with mind-body interventions.[15] However, although pain is a widespread problem in haemophilia, there are no published guidelines for the physiotherapy of management of chronic arthritic joint pain in this population.

1.1 | Objective

This review aims to evaluate and appraise the current evidence of the effects of physiotherapy interventions on (a) pain intensity, (b) quality of life and (c) function in PWH.

2 | METHODS

2.1 | Protocol and registration

The protocol was registered with the International Prospective Register of Systematic reviews (PROSPERO number: CRD42018116482). Reporting is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[16]

2.2 | Eligibility criteria

Study design for inclusion was those described as randomized controlled trials and quasi-experimental studies including controlled studies, before and after and interrupted time studies, comparing to no intervention/routine care group or between group comparison of one treatment intervention against another.

Studies describing any physiotherapy/rehabilitation/physical therapy intervention that had pain intensity, functional outcomes and health related quality of life as outcome measures were included.

Studies with participants of any age with a diagnosis of mild, moderate or severe haemophilia (A or B), and/or haemophilic arthritis were included. Those with participants with a diagnosis of an inhibitor (antibody to factor VIII or IX) and co-morbidities were not excluded. There was no restriction in country or care settings for studies.

Studies that investigated joint disease or pain as a result other inherited bleeding disorders such as von Willebrand disease were excluded.

2.3 | Information sources

A systematic search of the literature was conducted from the date of database conception to 20/07/2018, with a follow-up search again on 07/09/2018 (PML). The approaches used were as follows:

1. AMED (EBSCO), CINAHL (EBSCO), EMBASE (OVID), MEDLINE (OVID) and PEDro
2. Cochrane central register of controlled trials
3. Trial registries—clinicaltrial.gov, international trials registry, EU clinical trials register
4. Grey literature
5. Hand searching key journals
6. Checking reference lists of previous related systematic reviews in haemophilia
7. Hand searched abstract book of EAHAD congress (European Association of Haemophilia and Associated Disorders) 2000-2018 and WFH (World Federation of Haemophilia) world congresses 2000-2018

Only studies published in the English language were included.

2.4 | Search strategy

Figure 1 details the search strategy used across each database. Iterative refinement of the search strategy was achieved after multiple practice searches using potential search terms and associated subject headings. The university version of OVID and EBSCO search platforms maps to subject headings by default. The search strategy was discussed in detail and endorsed by the University librarian (AE-J).

2.5 | Study selection

One reviewer (PML) independently carried out the search strategy on the listed databases. Results were saved, duplicates removed and

FIGURE 1 Search strategy of terms for all databases [Colour figure can be viewed at wileyonlinelibrary.com]

Database/register	Search years	Search terms
AMED (EBSCO)	1985- present	#H(a)emophilia AND physio*/ physical*-therapy
CINAHL (EBSCO)	1961- present	#H(a)emophilia AND physio*/ physical*-therapy
EMBASE (OVID)	1976- present	#1 exp h*emophilia #2 exp pain
MEDLINE (OVID)	1964- present	#3 1 AND 2 #4 exp physio*/physical*-therapy #5 exp manual therapy or exp manipulative medicine #6 exp hydrotherapy or exp "aquatic exercise" #7 exp electrotherapy or exp "electrophysical agents" #8 exp rehabilitation or "home rehabilitation" or "rehabilitation medicine" or "exercise supervised" or "exercise unsupervised" #9 exp "patient education" #10 4 or 5 or 6 or 7 or 8 or 9 #11 3 AND 10 #12 "randomi*ed controlled trial" or "controlled trial" or randomi*ed #13 11 AND 12 (filter limits Full Text and English Language)
PEDro		#H(a)emophilia
www.clinicaltrials.gov		#H(a)emophilia AND physio*/ physical*-therapy
International Trials registry http://apps.who.int/trialsearch/		#H(a)emophilia AND physio*/ physical*-therapy
EU Clinical Trials Register www.clinicaltrialsregister.eu		#H(a)emophilia AND physio*/ physical*-therapy

then imported to the Rayyan platform,[17] enabling two reviewers (PML, DS) to independently review titles and abstracts whilst blinded from each other. Once each reviewer had completed their check, the abstracts were unblinded. We compared those which had been accepted, rejected and were undecided by both reviewers, and discrepancies between reviewers (n = 2) were discussed and a consensus reached.

Full texts of agreed abstracts were retrieved and evaluated independently (PML, DS) to determine eligibility for inclusion in the systematic review.

2.6 | Data collection process

A data extraction proforma was developed using the Cochrane Airways group template (https://airways.cochrane.org/data-collection). One reviewer (PML) extracted data studies, and a second reviewer (DS) checked extracted data for accuracy. One author was contacted for further information, and data were received.[18]

2.7 | Data items

Information extracted from each trial included study design, participant information, interventions, comparison interventions, outcome measures (pre- and postintervention, follow-up if available), results including pain, function and quality of life.

2.8 | Risk of bias in individual studies

The Cochrane Risk of Bias assessment tool was used to assess included papers and was carried out independently by two authors (PML, DS). Criteria of unclear, low or high risk of bias were assigned against selection bias, performance bias, detection bias, attrition bias, reporting bias and any other identified bias.

2.9 | Methods of analysis

Cochrane collaboration software (RevMan version 5.3)[19] was used to collate and analyse study data.

Mean change from baseline to follow-up and standard deviation of mean difference (MD) was calculated for input into RevMan. Using a fixed effects model, mean differences ± 95% confidence interval (CI) per intervention were calculated. Studies were grouped into (a) physiotherapy intervention vs no intervention and (b) physiotherapy intervention A vs physiotherapy intervention B.

A narrative synthesis of the evidence was completed including the use of the GRADE approach in grading evidence quality.[20] The GRADE system uses eight criteria against which to assess the quality of evidence as either high, moderate, low or very low. They are (a) risk of bias, (b) inconsistency, (c) indirectness, (d) imprecision, (e) publication and (f) other (i. large effect, ii. dose response, iii. no plausible confounding—only these assessments permit an upgrade). All outcomes start on 'high' quality (those studies not an RCT start score

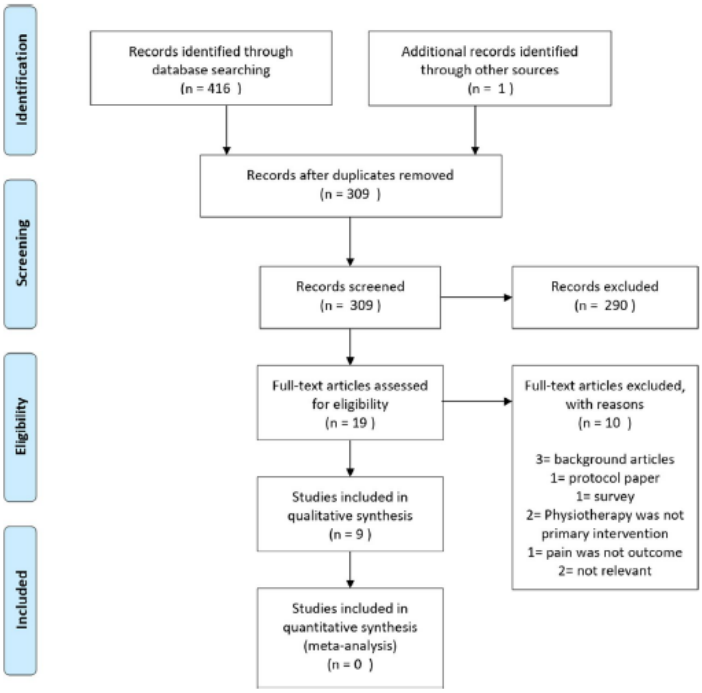

FIGURE 2 Flow chart of trial identification and selection for inclusion in review [Colour figure can be viewed at wileyonlinelibrary.com]

process on 'low'). They may then be downgraded one level per criteria if it is deemed to have a serious risk (–1) or very serious risk (–2).[21]

2.10 | Additional analysis

We were unable to undertake meta-analysis due to heterogeneity of the included studies.

3 | RESULTS

3.1 | Study selection

The search strategy identified 417 citations. Following removal of duplicates, 309 remained. Review of abstracts resulted in removal of 290, with further 10 being removed after full text review (Figure 2).

3.2 | Study characteristics

Nine studies were identified (Table 1). The number of participants per study ranged from 9[22] to 40.[23] The number of participants across all studies was 235. Of these, 60 were children (aged 9-13) and 175 were adults (aged 26-58). Severity of haemophilia was not specified for 70 participants. Of the remaining 165, 93 were identified as having a diagnosis of severe haemophilia, 50 moderate, 17 mild and 5 mild/moderate. One hundred and forty-nine participants were on prophylaxis and 46 were on-demand. Treatment regime was not stated for 40 people. Following GRADE assessment, all nine studies were rated as low/very low for quality of evidence.

3.3 | Interventions

Study intervention periods ranged from 3 to 15 weeks. Four trials had a RCT design.[18,23-25]

Four studies compared one physiotherapy intervention against another: passive joint mobilizations and exercise vs manual therapy and exercises in adults with haemophilic ankle arthropathy[22]; high intensity laser therapy (HILT) and exercise vs pulsed electromagnetic field and exercise in treatment of knee haemarthrosis in children[26]; home exercise programme and self-monitoring vs home exercise alone for haemophilic in adults with knee and ankle arthropathy[27]; and HILT and exercise vs placebo HILT and exercise in haemophilic arthropathy of the knee in children.[28]

Three studies in adults compared two physiotherapy intervention arms against a control group; manual therapy and exercise against patient education and exercise in haemophilic ankle

arthropathy,[24] with the same study design replicated for elbow arthropathy.[18] A third study investigated hydrotherapy against land-based exercise with a control group in haemophilic knee arthropathy.[23]

Two studies in adults compared one physiotherapy intervention with a control group; patient education and home exercises verses control on elbow, knee and ankle haemophilic arthropathy[25]; and fascial therapy vs control on knee and ankle haemophilic arthropathy.[29]

One study performed the intervention 3 sessions per week for 3 weeks,[29] with another not stating how many sessions were performed over 4 weeks.[23] Two studies performed the intervention for 2 sessions per week for 6 weeks,[18,22] and one study encouraged participants to do exercises 10 times a day for 8 weeks.[27] Another performed 2 sessions per week over 12 weeks[24] with another doing 1 session every 2 weeks for 12 weeks.[18] The participants in two studies received 3 sessions per week for 12 weeks[26] and another one session every 2 weeks for 15 weeks.[25]

3.4 | Risk of bias

All studies had an overall risk of bias (see Figure 3). Assessment of risk of bias found agreement between study authors was moderate (Cohen's *K* 0.51).

3.4.1 | Sequence generation

One study rated low risk as it described the use of a random number generation table for each participant.[27] Six studies were rated as unclear risk as sequence generation methods were not described. One paper rated high risk as participants were chosen for inclusion based on geographical location.[29]

3.4.2 | Allocation concealment

Two studies had a low risk with both describing opaque envelopes being distributed by someone unrelated to the study.[18,25] Six studies were rated unclear due to lack of detail on methods of concealment. One study rated high risk as participants were selected based on geography.[29]

3.4.3 | Blinding

Blinding of the participants was not possible in any of the included studies, and none of personnel were blinded in any study. Five studies used blinded evaluators to assess outcomes[18,22,24-26] and were rated low risk. Two studies rated unclear as they did not state if outcome assessment was blinded,[23,28] and two rated high risk as outcome assessment was completed by the same individuals delivering the intervention.[27,29]

3.4.4 | Incomplete outcome data

Four studies rated as low risk of attrition bias because each stated that all participants completed the intervention.[18,22,25,27] Five rated unclear as although they did not report dropouts, they also did not explicitly state that all had completed the intervention.[18,24,26,28,29] One study was rated high risk as although the authors reported three dropouts, they did not specify from which group they came.[23]

3.4.5 | Selective reporting

Three studies were rated high risk of selective reporting bias. One study failed to report on changes to bleeding frequency even though this was an inclusion criteria for the study.[26] Another describes an improvement in joint health with the Haemophilia Joint Health Score but include no data to support this[28] and another does not report on all of the elbow joints included in their study.[18] The six other studies had unclear risk of selective reporting bias.

No study was determined to have any source of other potential bias and therefore were rated as low.

3.5 | Data synthesis

Outcome measures for the nine trials are presented in Table 1. Although there were multiple outcomes measured across the trials, for the purposes of this review only those of pain intensity, quality of life and functional capability are included in this qualitative analysis, as per our protocol.

Data presented apply only to immediate postintervention assessments. All nine studies included an assessment for pain using the visual analogue scale (VAS). Two trials assessed health related quality of life (HR-QoL) using the A36 Haemophilia-QOL questionnaire.[22,25] Physical function was assessed in three studies using the 6-minute walk test (6MWT),[26] the 10 meter walk test (10MWT) and a modified functional reach test another.[27] No other studies measured function or HR-QoL.

Where trials compared two physiotherapy interventions against a control, results from each intervention were analysed individually against the control (physiotherapy intervention vs no intervention), as well as against each other (A vs B).

4 | PHYSIOTHERAPY VS NO INTERVENTION

Five studies were included in this comparison (Figure 4).[18,23-25,29]

TABLE 1 Summary of included studies with GRADE assessment

Trial and location	Methods	Participants	Intervention
Cuesta-Barriuso 2014[22] (Spain)	Quasi-experimental pre-post design	9 Adults with haemophilia A or B (mean age 35.8) and arthropathy in one or both ankles on prophylaxis. 3 bilateral ankle arthropathy, 5 with right ankle arthropathy and 1 with severe arthropathy left ankle. Severe: n = 8 (6 = SHA; 2 = SHB) Moderate: n = 1 (HA) Prophylaxis: n = 9 (2-3/wk 'according to medical criteria') Randomized into 2 groups: A: Passive joint mobilizations (n = 4) B: Manual therapy (n = 5)	6 wk study period 2 h per week (both groups) Both groups: infrared lamp start of session Group A: passive joint mobilizations and muscle exercises and proprioception Group B: had manual therapy (joint distractions) and muscle exercises and proprioception Both groups cryotherapy to finish session
Cuesta-Barriuso 2014[24] (Spain)	Randomized control pilot study	31 adults with haemophilia (mean age 35.29) and ankle arthropathy (6 unilateral and 25 bilateral arthropathy) Severe (n = 19) Moderate (n = 12) Randomized into 3 groups: Manual Therapy: n = 11(HA = 8; HB = 3) (Severe = 9; Moderate = 2) - Prophylaxis: n = 8 - On-Demand: n = 3 Education: n = 10 (HA = 9; HB = 1) (Severe = 7; Moderate = 3) - Prophylaxis: n = 7 - On-Demand: n = 3 Control group: n = 10 (HA = 9; HB = 1) (Severe = 3; Moderate = 7) - Prophylaxis: n = 2 - On-Demand: n = 8	12 wk study period Manual Therapy group: 2× 60 min per session per week Thermotherapy, ankle joint traction, passive muscle stretching gastrocnemius, Isometric and resisted exercises, proprioception exercises, local cryotherapy Education and exercise group: (6× 90 min sessions once a fortnight). Theory: ankle anatomy/biomechanics, joint bleeding, synovitis, arthropathy, proprioception, pain and mobility Practical: Ankle ROM exercises, strengthening exercises, exercise for mobility and pain management, proprioception exercises. Encouraged to walk, cycle and swim. Group support and Q&A feedback throughout
Cuesta-Barriuso 2017[25] (Spain)	Randomized controlled trial	20 adults with haemophilia (mean age 30.95) with at least one joint affected by haemophilic arthropathy. Severe: n = 10 Moderate: n = 3 Mild: n = 7 (HA = 16; HB = 4) Prophylaxis: n = 7 On-Demand: n = 13 Randomized to 2 intervention arms: Control: n = 10 (HA = 9; HB = 1) (Severe = 2; Moderate = 3; Mild = 5) Prophylaxis: n = 2 On-Demand: n = 8 Education with home exercise programme (HEP): n = 10 (HA = 7; HB = 3) (Severe = 8; Mild = 2) Prophylaxis = 5 On-Demand = 5	15 wk study period Educational sessions every 2 wk for 60 min alongside home exercise programme: Control group advised to continue with the same daily professional and sporting routines that they had been following *Education/HEP:* Theory: anatomy/biomechanics elbow, knee and ankle joints, haematoma management, exercise theory, joint bleeds, synovitis and arthropathy, proprioception, physical activity and sport. Practical: muscle stretching for the upper and lower limbs, strengthening exercises for quadriceps, hamstrings, biceps/triceps and calves, proprioception exercises, encouraged to do 20 min walk per day

Outcomes	Notes	GRADE assessment
Pain intensity ankle: VAS HR QoL: A36 Hemophilia QoL questionnaire Ankle ROM: Dorsi-, plantar-flexion, inversion, eversion Proprioception: Romberg's test	Not stated what baseline was for participants in each group (ie how many ankles (uni-or bilateral)—were affected in each individual)	Low ⊕⊕OO
Calf Strength: Calf circumference Ankle ROM: Dorsi-, plantar-flexion, inversion, eversion Ankle pain: VAS	Authors note that there were differences between the groups in terms of radiological deterioration, ROM and pain perception. Potential variance between groups associated with severity of haemophilia. Control group had mostly moderate and on-demand treatment participants, whereas both intervention arms had mostly severe and on prophylaxis. Participants handed records of home exercise compliance in every 2 wk—but it was not stated if these were fully complete.	Very Low ⊕OOO
Orthopaedic joint assessment: Gilbert Score Pain intensity ankle, knee, elbow: VAS Quality of life: A36 questionnaire Illness behaviour questionnaire (IBQ)	This appears to be the same group of participants that have already been enrolled in all of the authors previous papers. (? bias of results if participants have been exposed to previous interventions)	Low ⊕⊕OO

(Continues)

TABLE 1 Continued

Trial and location	Methods	Participants	Intervention
Cuesta-Barriuso 2018[18] (Spain)	Single blind randomized study	27 men with haemophilia (mean age 34.48 yr) and elbow joint arthropathy Overall: Severe (n = 17) Mild (n = 10) (HA = 22; HB = 5) Prophylaxis: n = 15 On-Demand: n = 12 Randomized to 3 groups- Manual therapy: n = 9 (HA = 6; HB = 3) (Severe = 8, Mild = 1) Prophylaxis = 7 On-Demand = 2 Education: n = 9 (HA = 8: HB = 1) (Severe = 6; Mild = 3) Prophylaxis = 6 On-Demand = 3 Control: n = 9 (HA = 8; HB = 1) (Severe = 3; Mild = 6) Prophylaxis = 2 On-Demand = 7	12 wk study period Follow-up assessment 6 mo after end of intervention. Manual therapy group 2× 60 min per session per week: Thermotherapy, elbow joint traction, elbow muscle stretching, joint compression technique, passive muscle stretching biceps/triceps, PNF of upper limb, local cryotherapy. Education group (90 min session every 2 wk, plus home exercise programme 20-30 min daily): Theory: anatomy/biomechanics of elbow, haematoma management, joint bleed, synovitis, arthropathy, proprioception, physical activity and sport. Practical: Elbow ROM exercises, strengthening exercises, exercise for mobility and pain management, proprioception exercises Control Group: usual routine
Donoso-Ubeda 2018[29] (Spain)	Non randomized, controlled before and after trial	16 men with haemophilia (mean age 40.69) and haemophilic arthropathy of the knee and ankle. Severe (n = 12) Moderate (n = 4) Prophylaxis: n = 16 Mean freq. every 2.44 d (±0.51) Mean dose FVIII/FIX = 2625±619.13 units 2 groups: Fascial therapy (n = 8) Control (n = 8)	3 wk study period 3× 50-60 min session per week. Control: advised to maintain same level and conditions of physical work and activity. Intervention arm: Fascial therapy No description given of patient position. All manoeuvres done on both lower limbs except thoracolumbar technique. Superficial and deep fascial release techniques.
Eid 2015[26] (Saudi Arabia)	Randomized Trial	30 boys with haemophilia (aged 9-13), with a bleed frequency in their knees of at least once a week. Moderate Haemophilia A: n = 30 Prophylaxis: n = 30 (No regime stated) Randomized to 3 groups: Low level laser therapy (LLLT) (n = 15) Pulsed electromagnetic field therapy (PEMF) (n = 15)	12 wk study period Both Intervention 3 times per week. Both groups had a physiotherapy programme as well as the study intervention. LLLT: applied to 5 points including medial and lateral side patellar tendon, medial and lateral side knee adjacent to patella and over suprapatellar pouch. Applied for 40 s to each point. PEMF: solenoid adjusted to be over both knee joints. Parameters of treatment programme selected and adjusted as a frequency of 15 Hz, intensity of 20 gauss for 20 min. *Physical therapy program* In acute haemarthrosis: cold packs, isometric exercises. In subacute: isometric and isotonic exercises given additionally. Chronic arthropathy: hot packs, strengthening, proprioception and stretching exercises. All groups had a home programme

Outcomes	Notes	GRADE assessment
Safety of intervention Elbow ROM: Flexion/ extension Arm circumference Biceps strength Pain intensity elbow: VAS	Baseline imbalances between groups: more people with mild haemophilia in the control group (6) than the Manual therapy group (1). Median VAS at baseline in education and control group was 0. Results presented in median and IQR instead of mean and SD—emailed authors to request data in mean/SD which was made available	Low ⊕⊕OO
Joint health: Haemophilia joint health score 2.1 Hamstring flexibility: Finger to floor test Lumbar mobility: Schober test Pain intensity right and left knee and ankle in weight and non-weightbearing: VAS	No randomization	Very Low ⊕OOO
Pain intensity knee: VAS ROM knee Flexion/ Extension Swelling: Tape measure around knee Physical fitness: 6 min walk test (6MWT) Laboratory investigations: Erythrocyte sedimentation rate Complete blood count including white blood cells	Poor description of intervention especially the physiotherapy programme. It was unclear when the laser was delivered in the session. There are ethical concerns about why the investigators would expose both knees to PEMF as it did not state if both were affected (when the LASER group only treated one knee). Unclear if rate of haemarthrosis continued to be once per week throughout intervention period. No description of how acute, sub-acute haemarthrosis was assessed	Low ⊕⊕OO

(Continues)

TABLE 1 Continued

Trial and location	Methods	Participants	Intervention
El-Shamy 2016[28] (Saudi Arabia)	Single-blinded, placebo controlled randomized trial	30 boys with Haemophilia A (aged 9-13) with bilateral knee haemarthrosis. Severity of haemophilia not stated. Prophylaxis: n = 30 Regime not stated Randomized into 2 groups: Laser therapy (n = 15) Sham Laser group (n = 15)	3 mo study period. 3× 1 h sessions per week. Both groups: received a 'traditional' physiotherapy programme that included hot packs, muscle stretching and strengthening exercises, proprioceptive training, balance and gait training. Laser group: Laser from HIRO device. Positioning: knee flexed to 30 degrees. Initial phase performed with fast scanning for total of 400 J. Intermediate phase—applied hand piece to total 10 points (3 in medial knee, 2 in lateral knee and 3 above patella, and 2 below patella) with a fluency of 10 mJ/cm^2 and a time of 14 s at each point for a total of 150 J. Final phase—same as initial phase, except that slow manual scanning was used with a total energy of 200 J. Sham Laser group: HILT machine switched on with a visible light beam only—all parameters set up without switching the start position of the machine
Goto 2014[27] (Japan)	Prospective, controlled, randomized non blind comparative stud	32 men with haemophilia (mean age 41.8) with arthropathy in knees or ankles. Recruited across 4 sites Overall: Severe: n = 27; Moderate/mild: n = 5 HA = 26; HB = 6 Randomized into 2 groups: Home exercise programme with self-monitoring (n = 16) Severe = 13; Moderate/mild = 3 Prophylaxis = 14 On-Demand = 2 Home exercise alone (n = 16) Severe = 14; Moderate/mild = 2 Prophylaxis = 11 On-Demand = 5	8 wk study period. Both groups: given home exercise programme. Only difference is the participants in the intervention arm could review their progress on their monitors, whereas the control arm group could not. Home exercise programme—guidance about strengthening knee extensors, static stretching for knee flexors and standing balance training. Advice on promotion of physical activity given by physio to improve knee function. Knee extension strength training, static stretches and balance training Advice on leading an active life and doing non-contact sports were recommended for improving physical activity. ** physio recommended the exercise most appropriate to the physical condition of each patient to be done 10 times per day Self-monitoring: Participants were equipped with display activity monitors and feedback system via internet and mobile phone. When participants accessed the server to data input—feedback results appeared with time in form of graphs and tables. The number of times performed exercises, physical activity, bleeding frequency and injection of factor were recorded
Mazloum 2014[23] (Iran)	Quasi-experimental and prospective trial with a non-randomized pretest-post-test control group	40 people with haemophilia under 50 y old with impaired knee joint ROM. All severities—although exact numbers not stated. HA or HB—not stated Prophylaxis—not stated Randomized to 3 groups: Hydrotherapy (n = 14) Land-based exercise (n = 13) Control Group (n = 13) Clotting factor taken before participation in activity (dose not stated) (Average age in each study group = 33 y)	4 wk study period. Hydrotherapy: Warm up (5 min)—co-ordinated and rhythmic movement of lower limb in water. Exercises (30-45 min) for hamstrings stretching, quadriceps strengthening, from isometric to isotonic. Cool down (5 min) gentle stretching Land-based exercise: Warm up (5 min) simple stretching exercises for muscles surrounding knee. Main part (30-45) hamstrings stretching, quadriceps strengthening, progressing from isometric to isotonic. Cool down (5 min) of gentle stretching Control: Not stated what was advised

Note: GRADE Key: ⊕⊕⊕⊕—High Quality—Confident that true effect lies close to that of estimate effect; ⊕⊕⊕O—Moderate Quality—moderately confident in the effect estimate; ⊕⊕OO—Low Quality—confidence in effect estimate is limited; ⊕OOO—Very Low Quality—Very little confidence in the effect estimate.

Outcomes	Notes	GRADE assessment
Pain intensity knee: VAS Functional capacity: 6MWT Gait assessment: Stride length, step length, velocity and cadence—using GAITRite system		Very Low ⊕OOO
Self-efficacy for exercise questionnaire: Questionnaire not stated Exercise adherence questionnaire: Questionnaire type not stated Quadriceps strength: using hand held dynamometer ROM: Ankle—plantar-, dorsiflexion Knee—flexion/ extension Function: Modified functional reach test 10 m gait time Pain intensity: VAS Physical Activity levels— using activity monitor	Baseline imbalances of participants joint disease—ankle arthropathy was a much worse issue in the whole cohort even though the exercise plans carried out by participants was aimed at improving knee function. Unclear who delivered the programme to intervention group across the 4 sites and how the programme was delivered	Very Low ⊕OOO
Pain intensity knee: (VAS) Knee ROM: Flexion and extension	Number of sessions per week was not stated. 43 participants started study, but 3 dropped out (did not state from which group)	Very Low ⊕OOO

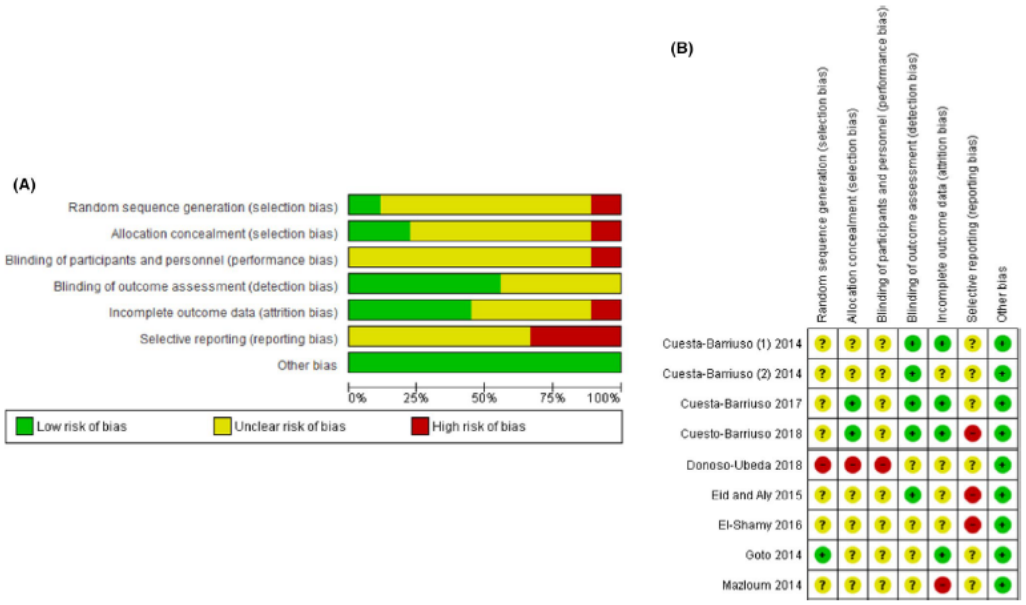

FIGURE 3 A, Risk of bias graph—author assessed risk of bias across all studies. (B) Risk of bias summary—author assessed risk of bias for each study [Colour figure can be viewed at wileyonlinelibrary.com]

4.1 | Primary outcomes

4.1.1 | Pain

All five trials included assessment of pain intensity using the visual analogue scale (VAS), with improvement in pain reported as a decrease in the VAS score. All were conducted on adults over 18 years of age, and apart from one study,[29] all were RCT's.

Elbow

There was no clear benefit on pain intensity when using manual therapies and education on elbow pain, MD −0.30 VAS (95% CI −0.92 to 0.32) or when using home exercises and education, MD −0.01 VAS (95% CI −0.34 to 0.36).

Knee

There was no clear benefit on pain intensity when using home exercises and education, MD −0.75 VAS (95% CI −2.13 to 0.63) or fascial therapy, MD −0.87 VAS (95% CI −2.81 to 1.07). Both hydrotherapy and land exercises were beneficial to knee pain intensity compared to no intervention. Hydrotherapy vs no intervention had a slightly stronger effect on pain intensity, MD −2.0 VAS (95% CI −3.28 to −0.72) compared to land-based exercise vs no intervention, MD −1.2 VAS (95% CI −2.54 to 0.14).

Ankle

There was no clear benefit on pain intensity with home exercises and education MD −0.55 VAS (95% CI −2.37 to 1.27), MD −0.3 VAS (95% CI −1.2 to 0.6), or with manual therapy and exercise MD 0.06 VAS (95% CI −1.47 to 1.6). Fascial therapy showed a small positive effect of the intervention on right ankle pain intensity, MD −0.76 VAS (95% CI −1.39 to −0.13), but this was a study with high risk of bias.

4.2 | Secondary outcomes

4.2.1 | Quality of life

Only one study[25] investigated the effects of patient education and home exercise programme (n = 10) compared to no intervention (n = 10) on patient reported quality of life. It is not clear if there is any beneficial effect of the intervention on quality of life, MD QoL 18.50 (95% CI −2.25 to 39.25).

4.2.2 | Function

None of the studies measured function as a outcome of intervention.

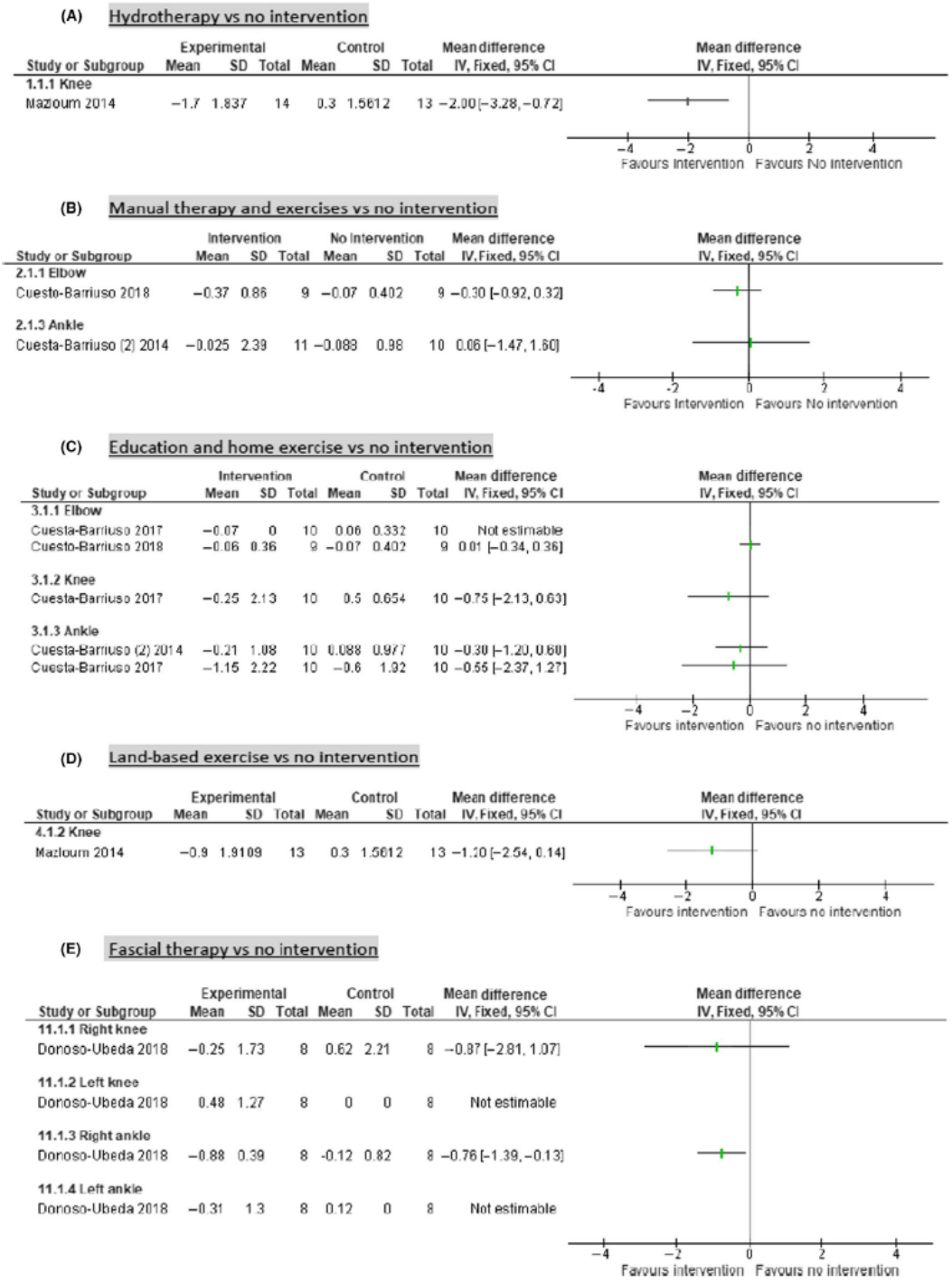

FIGURE 4 Comparison of physiotherapy intervention vs no intervention—Pain [Colour figure can be viewed at wileyonlinelibrary.com]

5 | PHYSIOTHERAPY INTERVENTION A VS PHYSIOTHERAPY INTERVENTION B

Seven studies were included in this comparison (Figure 5).[18,22-24,26-28]

5.1 | Primary outcomes

5.1.1 | Pain

All seven trials included assessment of pain intensity using the visual analogue scale (VAS), with improvement in pain reported as a decrease in the VAS score. Five were conducted on adults over 18 years of age, and two on children between the ages of 9 and 13.

Elbow

There was no clear demonstration of benefit for manual therapy and exercise over education and home exercises for elbow pain MD −0.31 VAS (95% CI −0.92 to 0.3).

Knee

Hydrotherapy has a more positive effect on knee pain than land-based exercise, MD −2.6 VAS (95% CI −4.02 to −1.18). LASER and exercise had a more positive effect on pain intensity than either sham laser left knee, MD −1.73 VAS (95% CI −2.23 to −1.23) right knee, MD −1.61 VAS (95% CI −2.09 to −1.13), or PEMF and exercise MD −1.07 VAS (95% CI −1.84 to −0.3).

Ankle

There was no clear benefit on pain intensity when comparing mobilization and exercise with manual therapy and exercise MD 0.4 VAS (95% CI −3.34 to 4.14), or manual therapy and exercise with home exercises and education MD 0.18 VAS (95% CI −1.38 to 1.75).

Pain (knee and ankle combined)

It is not clear if there any beneficial effect on knee and ankle pain of a self-monitoring home exercise programme compared to an exercise programme alone, MD 0.62 VAS (95% CI −0.37 to 1.61).

5.2 | Secondary outcomes

5.2.1 | Quality of Life

Only one study[22] investigated the effect of a joint mobilization and exercise intervention (n = 5) vs a manual therapy and exercise intervention (n = 4) on patient reported quality of life. The A-36 Haemophilia-QoL questionnaire was used. This is a 36 item questionnaire with a score range of 28-138 (higher score meaning better QoL). It is not clear if there is any beneficial effect on Quality of life from either intervention arm, MD −9.1 QoL (95% CI −47.2 to 29).

5.2.2 | Function

Three studies included a measure of function as an outcome measure of intervention.

It is not clear if there is any beneficial effect on function as measured by the 6MWT with LASER and sham LASER, MD 29.33 minutes (95% CI −9.48 to 68.14), or LASER and exercise compared to PEMF and exercise, MD 14.47 minutes (95% CI −21.34 to 50.38).

It is not clear if there is any beneficial effect with self-monitoring and exercise vs exercise alone on modified reach test, MD 0.1 cm (95% CI −7.64 to 7.84) or on 6MWT, MD 0.4 seconds (95% CI −0.84 to 1.64).

6 | DISCUSSION

This review presents the current evidence of trials utilizing a variety of physiotherapy approaches, with potential effect on pain intensity, quality of life and functional ability in PWH. It demonstrates that currently, there is low/very low quality of unclear evidence of effectiveness of many physiotherapy interventions on these outcomes.

The studies included in this review highlight the wide range of interventions being studied. They included joint manual therapy, passive joint mobilizations, exercise interventions, patient education, high intensity laser therapy (HILT), pulsed electromagnetic field treatment, hydrotherapy and fascial release therapy.

Pain is an issue that many PWH state is one of their major concerns,[30] yet no study included in this review defined pain as a specific inclusion criteria or ascertained if the presence of pain was of concern to participants. This may indicate assumptions made on the presence of pain based only on having haemophilia and/or arthropathy. Across many of the studies, the small differences in pre- and postintervention pain (VAS) highlight only a small change after intervention. It is unclear if this is due to a low pain VAS report preintervention (ie they had less/minimal pain upon starting the intervention) or a lack of effect of the intervention.

Only two studies included quality of life assessment,[22,25] and three included an assessment of function.[26-28] The minimal evaluation of psychological and social aspects of well-being alongside pain or basic joint function (such as ROM) makes no clear distinction of what the interventions mean to the individual taking part.

Physiotherapy trials can be considered a 'complex intervention'—that is, an intervention containing several interacting components. Dimensions of complexity can include the following: the number of and interactions between components in the same experimental and control interventions, the number and difficulty of behaviours required by those delivering or receiving the intervention, number of groups targeted by the intervention, the number and variability of outcomes being measured and the degree of flexibility or tailoring of the intervention permitted.[31] Haemophilia and its associated co-morbidities is a highly complex presentation, and as a result, any physiotherapy intervention would be, by-proxy, a complex intervention. Trials described here take no account of the potential complexity of the condition or the

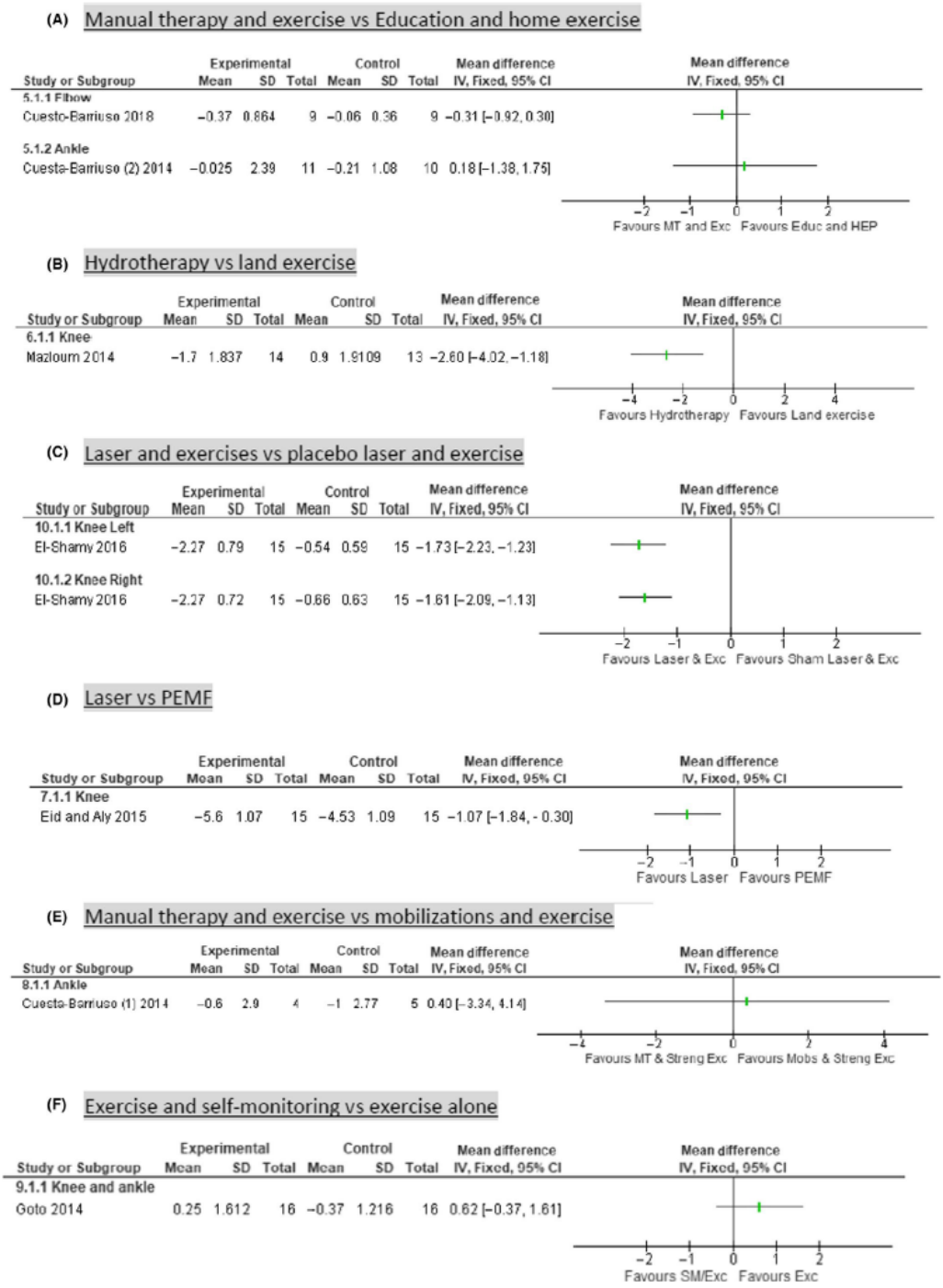

FIGURE 5 Comparison of physiotherapy intervention 'A' vs physiotherapy intervention 'B'—Pain [Colour figure can be viewed at wileyonlinelibrary.com]

intervention, thereby making it difficult to evaluate them in their practical effectiveness or to identify how they may be exerting their effects.

Education showed little positive effect when used in conjunction with exercise or manual therapy. It is not clear from the studies how the teaching curriculum was developed. Including health education without consideration for potential behaviour change models of action limits evaluation of how any education provision may be having its effect.[32]

Previous systematic reviews share some similarities to this review. However, the quality of some of those reviews, as well as their results and recommendations, differs to those presented here. Although described as a systematic review, an evaluation of exercise and sport in the treatment of PWH[33] lacked clear inclusion criteria as well as systematic analysis or comparison of data. In a narrative review of physical exercise, pain and musculoskeletal function in PWH Schäfer and colleagues[34] described the data for intervention effectiveness and concluded that exercise promoted a reduction in pain, improved ROM and strength in PWH. However, mean change from baseline together with confidence intervals was not reported or compared. They also reported low risk of bias in three studies that we assessed as having high risk,[22,23,27] although this may be due to different assessment tools being used.

A recent Cochrane Review on Exercise for haemophilia[35] was well conducted and included a broader range of outcomes in their analysis than this review. Similar to us, they noted major issues on study quality and stated that although exercise was likely safe, they urged caution with results as they stand.

Two further systematic reviews focussed on the treatment of chronic haemophilic ankle arthropathy[36] and physiotherapy in the treatment of haemophilic arthropathy.[37] The focus of the analysis in both was on the physiotherapy intervention itself rather than comparing the effects of those interventions on specific identified outcome measures. This makes it difficult to infer efficacy of any one specific intervention on measures such as pain and function. In contrast to our findings, the second review reported good study homogeneity, but it was not clear how this was evaluated.

Overall, the methodology and reporting quality of many of the included trials were poor. No study rated as high when being assessed for overall risk of bias. Many failed to provide details on randomization or participant allocation as well as appearing to omit some data in their overall results. High degree of trial heterogeneity was identified for both participants (severity of haemophilia, age range, location and number joints affected) as well as interventions (varied time frames for delivery, intervention components and outcome measures). Thus meta-analysis was not possible. Participant numbers were low for all included trials, and four of the trials were randomized pilot studies.[18,22,24,29]

Although overall safety from physiotherapy interventions was not included as an outcome for this review, it is acknowledged that physiotherapy interventions themselves may negatively influence pain, function and QoL. Safely participating in a rehabilitation programme is paramount from a haemostatic perspective as well as the perception of safety of the individual taking part. The limited detail on participant prophylaxis regimes limits further extrapolation of findings for others regarding intervention planning and safety, as does the heterogeneity of severity of disease in participants. None of the trials included only people with severe haemophilia—an important factor in considering the implications of potential effects of physiotherapy interventions, as severe haemophilia remains a diagnosis most likely to result in multi-joint arthropathy and pain. Further studies should seek to include all participant diagnostic and treatment information when reporting and publishing their results.

No studies appear to have involved PWH in the trial design, nor evaluated any qualitative measure of participation in such trials. As a rare disease, many PWH can be considered experts not just in their condition, but also in potentially identifying what matters to them in respect of rehabilitation interventions.

A strength of this review is the process of using two blinded reviewers throughout the process. Unlike many of the previous similar systematic reviews, we analysed the data to produce confidence intervals (CI's) and mean difference (MD) figures, allowing a good visual representation of effectiveness. A limitation is that we were unable to proceed to complete a meta-analysis of the data from any of the included studies. This precludes any clear recommendations for the use of physiotherapy interventions in the management of pain in haemophilia.

Better design of trials is required and should include PWH in the process. Specific and defined inclusion criteria relating to haemophilia disease severity, as well as pain as a self-reported symptom, are needed to better assess efficacy of any interventions.

The current use of only VAS in measuring pain intensity requires further scrutiny. Pain as a multi-modal, personal, lived experience is poorly evaluated when measuring intensity alone.[38] Further trials need to focus on how interventions may be designed to improve the physical, social, psychological and functional ramifications of a life-lived with pain.

7 | CONCLUSION

This systematic review highlights that there is currently an unclear demonstration of evidence for the use of physiotherapy interventions for pain management in people with haemophilia. LASER with exercise and hydrotherapy/land-based exercise appears to have some positive effect on knee pain in PWH. However, caution must be taken with this recommendation due to poor quality reporting and high risk of bias in both trials. It is not possible to make recommendations on any other physiotherapy intervention in the management of pain in haemophilia. Improved trial design and methodology will allow this emerging body of research to be effectively collated and compared, to further develop effective interventions for pain in haemophilia.

ACKNOWLEDGEMENTS

We wish to express our thanks to librarian Anna El-Jouzi for her help and guidance in the development of the search strategy.

CONFLICT OF INTERESTS

None of the authors have interests which may be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTION

PML, DS and MH contributed to the study design. PML and DS contributed to data extraction and analysis for the review. All authors contributed to the development and review of the manuscript.

DISCLAIMER

This publication presents independent research funded by the NIHR. The views expressed are those of the authors and not necessarily of the NHS, the NIHR or the Department of Health and Social Care.

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Appendix D - St. George's University Research Ethics Committee confirmation letter

St. George's Research Ethics Committee
Joint Research and Enterprise Services
Ground Floor, Jenner Wing
St. George's University of London
Cranmer Terrace
London
SW17 ORE
Phone: 0208 266 6073
Email: sgulrec@sgul.ac.uk

Paul McLaughlin
[redacted]

11th January 2019

Dear Paul,

Study Title:	Exploring the views and opinions of people with haemophilia and haemophilia healthcare professionals, in the management of chronic lower limb joint pain – a focus group approach
REC reference (please quote this in all future correspondence):	2018.0309
Co-investigators/collaborators:	Professor Michael Hurley
Amendment number:	Amendment 1
Amendment date:	10/01/2019

The St. George's Research Ethics Committee (SGREC) reviewed the above on 9th January 2019. Thank you for attending the meeting to answer the Committee's questions. The Research Ethics Coordinator within The Joint Research and Enterprise Service (JRES) reviewed the above amendment on behalf of the St. George's Research Ethics Committee (SGREC). I am pleased to inform you that your amendment has been approved.

The list of amendment documents reviewed and approved by the St George's Research Ethics Committee (SGREC) under requirements of the UK Policy Framework for Health and Social Care Research are as follows. If you believe any of the documents below are incorrect and a different version should have been reviewed by the committee, please contact the Research Ethics Officer (sgulrec@sgul.ac.uk) as soon as possible:

Document Name	Version	Date
SGREC Application form	V2	10/01/2019

After amendment approval

Amendments

If you have any further amendments to your project in the future, you must notify the Committee prior to implementing them. If you are unsure whether your amendment needs to be notified to the SGREC, please contact the Research Ethics Coordinator in the first instance (sgulrec@sgul.ac.uk). Amendments include changes to the study team, study design or supporting documents, including minor changes to text or format/layout.

Annual Progress Report

You are required to submit an annual progress report within 30 days of the anniversary of your original ethical approval letter.

If your study is completed within a year of you first obtaining ethical approval, you should complete a declaration of the end of a study instead.

The annual progress report is a condition of your ethical approval. If you do not submit an annual progress report, your study will be assumed to be closed, and ethical approval will be stopped.

Declaration of the End of a Study

You need to notify the Committee within 90 days of the termination of your study and within 15 days if you have terminated the study early.

All forms can be found on the SGREC area of the SGUL portal or can be obtained from the Research Ethics Coordinator (sgulrec@sgul.ac.uk).

The SGREC pages on the SGUL portal also provide guidance on these topics, and is regularly updated in the light of changes in reporting requirements or procedures.

If you have any further questions or queries please do not hesitate to contact me.

I wish you well in your research.

Appendix E - Recruitment Poster for Focus groups

Do you have severe haemophilia and joint pain?

Are you interested in being part of a research project?

The project: Exploring the views and opinions of people with haemophilia on the management of chronic lower limb joint pain

Why: We want to understand better what it is like to live with joint pain and haemophilia.

What have you done to try and help your pain? Did it work?

What do people with haemophilia and joint pain think about the idea of exercise for pain management?

How: We will do an interview with you at a time and location that suits you

We would like to hear from you if:

- you are between 18-30 years old
- have severe haemophilia A or B
- are independently mobile
- have had pain in the any of the joints in your legs for more than 3 months

If you are interested in taking part in this study – please contact **PAUL MCLAUGHLIN**

[redacted]

We will reimburse you for your travel costs and for your time in attending the meeting.

St George's University of London

THE HAEMOPHILIA SOCIETY

Proudly supporting people affected by a genetic bleeding disorder

Appendix F - Focus Group – Participant information sheet

PARTICIPANT INFORMATION SHEET

Study Title:
Exploring the views and opinions of people with haemophilia on the management of chronic lower limb joint pain – a focus group approach

Study sponsor:
Royal Free London NHS Foundation Trust

St George's Research Ethics Committee ID: 2018:0309

Invitation

You are being invited to take part in a research study that is being conducted in the UK in people with severe haemophilia who have chronic joint pain. Before you decide whether or not to take part, it is important for you to understand why this research is being done and what it will involve. Please take the to read the following information carefully before you decide whether you would like to participate. Please ask us if there is anything that is not clear or if you would like further information.

What is the purpose of this study?

Chronic joint pain is a problem for many people who have knee and ankle arthritis as a result of their haemophilia. Many people who have this pain have reported that they feel it is poorly managed and that they struggle to function well with their pain. For some of the other types of arthritis (such as osteoarthritis) we know that rehabilitation can have positive effects on pain. As yet we cannot say if it could be effective for people with haemophilia.

In order to try and design a rehabilitation programme that may help manage pain in haemophilia, we need to try and understand what people with haemophilia and joint pain think about the idea of exercise for pain.

We are going to have two focus group meetings with patients. We want to understand better what it is like to live with joint pain and haemophilia, things that people may have tried that worked and didn't work. We want to try and get a clearer idea of things to consider when we come to design the main rehabilitation trial.

The main aim of this study is to discover what matters most to people with joint pain and haemophilia. This information will be used in the next stage of the project to help design the rehabilitation trial.

Why have I been chosen?

You have been chosen because you have a diagnosis of severe haemophilia A or B, and have told us that you have chronic pain in the joints of your lower limbs.

Do I have to take part?

No. Your participation in this study is entirely voluntary and you can stop any time you wish, without providing a reason and without having any consequences for your future medical treatment. If you decide to take part in this study you will be asked to sign a consent form. You will be given a copy of the consent form to keep, along with this information sheet.

What will happen to me if I take part?

If you decide to take to part, you will be asked to contact the lead researcher, Paul McLaughlin, by phone or email. He will then contact you to check some baseline information. If you are able and still willing to take part, you will be sent an invitation letter to attend the focus group in your local area (either London or Sheffield).

When you attend on the day of the focus group, you will be asked to sign a consent form. Every member of the group will have to do the same. We expect there to be 6-10 people per group. The group meeting will last between 90 mins and two hours and all of the discussions will be recorded.

What do I have to do?

You will be asked to attend a focus group meeting with other people with haemophilia and joint pain. There will be 2 researchers in the room with the group. They will be helping to generate discussion between all of the participants and we want you to play as active a part in this discussion as you can. You will not be forced to talk or share things you do not feel comfortable with.

We want to hear and understand your opinion and experiences in the discussion, as this will help us design the next step of the trial for people with joint pain and haemophilia.

What are the other possible disadvantages and risks of taking part?

There may be a small possibility that in the course of the group you may feel that some sensitive issues are touched upon (eg about living with pain). If at any time you feel upset or want to leave the room, the second researcher can be there for support. If you feel you require any further support about any of the issues raised by the group, you are encouraged to speak to a healthcare professional who will be able to assist you.

What are the possible benefits of taking part?

This study will not help you directly. However it will help in the design and implementation of a trial using rehabilitation for pain management for people with haemophilia.

What happens when the research stops?

The research study will not involve any further commitment from you after the focus group has ended.

What if I change my mind?

Your participation is entirely voluntary and you are free to withdraw at any time, without giving any reason, without your medical care or legal rights being affected. Data collected up to the point of withdrawal will be used in the study.

Will my taking part in this study be kept confidential?

Yes. All the information about you in this study will be kept confidential.

The recording of the focus group will be written up and then checked against the audio recording. Any personal information included here (such as name) will only be seen by the research team. No personal data will be included in any reports or write ups. Once the recordings from the group have been analysed, the recorded version will be deleted.

The consent form (that will have your name on it) will be held securely at the lead researchers office and will only be accessible by the lead researcher.
No other information will be collected by the research team about you.

What will happen to the results of this study?

The results of this study will be available after it finishes. The information and data gathered as a result will usually be presented at a scientific conference and be written up in a medical journal. No personal identifying information will be included in any of these reports or publications. It is likely we will also share the results of the study through the Haemophilia Society, so it can be shared throughout the UK for patient information and benefit.

Should you wish to see the results of have a copy of any publications, please ask a member of the research team.

Who is organising and funding this study?

This research project is being undertaken as part of a clinical doctoral research fellowship, and forms part of a PhD being undertaken by Paul McLaughlin at St George's University of London. It is funded by the National Institute of Health Research.

The study is being sponsored by the Royal Free London NHS Foundation Trust and will act as the data controller for this study. This means that Royal Free London NHS Foundation Trust is responsible for looking after your information and using it properly. They will keep any identifiable information about you for 5 years after the study has finished.

You can find out more about how we use your information https://www.hra.nhs.uk/information-about-patients/

Who has reviewed the study?

This study has been reviewed and given favourable ethical opinion by St. George's University Research Ethics Committee: ID number 2018:0309.

What happens if there is a problem?

We would not expect you to suffer any harm or injury by participating in this study. If you are harmed by taking part in this study, there is no special compensation arrangement. If you are harmed due to someone's negligence then you may have grounds for legal action, but you may have to pay your legal costs. Regardless of this, if you wish to complain or have any concerns about any aspect of the way you have been approached or treated during the course of the consent process or the study the National Health Service Complaints mechanism is available to you. If you have any concerns regarding the care you have received or as an initial point of contact if you have a complaint, please contact the Patient Advice and Liaison Service (PALS) at the address given below:

PALS office: 020 7830 2174

PALS

Royal Free Hospital,

Pond Street,

London, NW3 2QG

Contact for further information

You are encouraged to ask any questions you wish to before, during or after your participation in the study. If you have any questions about the study, please contact Paul McLaughlin directly (details below). If you require any further information or have any concerns while taking part on the study please contact any of the following people:

Your researcher:
Paul McLaughlin

[redacted]

OR

[redacted]

THANK YOU FOR TAKING THE TIME TO READ THIS INFORMATION SHEET

Appendix G - Participant consent form – focus group

PARTICIPANT CONSENT FORM

(people with haemophilia)

Exploring the views and opinions of people with haemophilia on the management of chronic lower limb joint pain – a focus group approach
DOB:

INITIALS:

Research Ethics committee Ref:	
	Participant initials
I confirm that I have read and understood the information sheet version 1 dated xx xxx 2018 for the above study. I have had the opportunity to ask questions and I am satisfied with the answers.	
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected.	
I understand that information collected today in the group will be used to support other research in the future and may only be shared anonymously with other researchers associated with the research team.	
I understand that the discussions in the group today will be digitally recorded and typed up into a transcript for analysis by the research team. I am happy that anonymised quotations may be used in any publications that follow from this group.	
I consent to the storage of personal information for the purposes of this study. Any information that could identify me will be kept strictly confidential and that no information that could identify me will be included in study reports or any other publications.	
I voluntarily agree to be part of this research study.	

Name of Participant	Date	Signature
Name of person taking consent	Date	Signature

Version 1.0 dated: 17th October 2018

Appendix H - Focus Group topic guide – PWH

FOCUS GROUP TOPIC GUIDE: EXPLORING THE VIEWS AND OPINIONS OF PEOPLE WITH HAEMOPHLIA ON THE CURRENT AND POTENTIAL MANAGEMENT OF CHRONIC LOWER LIMB JOINT PAIN

1. **Introduction**

- Introduce self and study
- Emphasise non-judgemental position, discussion not a Q&A
- Assure confidentiality
- Check permission to use audio recorder
- Mobiles off
- Thank all the participants for attending, no right/wrong answers, views and experiences are what matter

2. **General background information**

Invite all of the participants around the room to introduce themselves (include age and where they are currently living).

3. **The lived experience of having chronic joint pain**

- First memories of joint bleeding
- How this was managed
- In and out of hospital
- When did first release had pain
- How many years
- How does it relate with their haemophilia
- How it affects their day to day life
- Effect on work, study, family life

PROBE

- Does it effect how active they are?
- How much
- Why?
- Would you like to do more

4. **Methods of pain management being used**

- What current methods are they using
- What previously have they done
- Why did they choose these
- PROBE
- Non medications such as illicit drug use, alcohol etc
- Did anything work well
- Why do they think it worked
- What did not work – why not
- What about help from haemophilia treaters (Dr's, nurses, Physios etc)
- Anyone else – GP?

5. **What is causing the pain**

- Why do you think your joints are painful (PROBE)

-structural
-psychological
-mood
-expectation/normal

- Have you noticed any particular things that happen to make you have more pain
- What is the relationship between these events and your pain
- Do you think your pain can be made easier/managed better

6. Using a rehabilitation intervention for joint pain in PWH

- what do you think about using exercise and activity to help pain
- what do you think may happen if you were to do this with your painful joint
- PROBE
  - Why do you think it would be ?bad
    have they been advised not to exercise – by who? Why?
  - Why do you think it may be good?
- What things are important for you to know to take part in something like this
-PROBE
  - Education
  - how long (how many weeks)
  - What do you think of exercising as part of a group
  - what kind of things you would be doing
  - where it would take place (is that important)
  - opinion of haemophilia Dr's
- Do you think it would be safe?
  - Bleed risk
  - more damage
  - more pain

7. Barriers and facilitators to a planned intervention

- what is important for us to tell potential participants of a group such as this
- What things are important to help it run well
- Why do think people may not want to come

...Nearly there – just one more topic to discuss to bring this to an end...

8. Outcomes to measures

We want to collect information about you before and after the intervention.

- What should we ask about to see if the group was helpful
- What matters most to you in trying to manage your pain on a daily basis

9. Anything else to add?

Have you any questions or thoughts to add about the things we have discussed here today?

10. Close the group – thank participants for their time and assure confidentiality once again.

11. Final thanks – give expenses form and complete receipt/bank details information for transfer of money for expenses.

Appendix I - Healthcare professional interview topic guide (Chapter 4 Qualitative study)

FOCUS GROUP TOPIC GUIDE: EXPLORING THE VIEWS AND OPINIONS OF HAEMOPHILIA HEALTHCARE PROFESSIONALS ON THE CURRENT AND POTENTIAL MANAGEMENT OF CHRONIC PAIN

1. **Introduction**

- Introduce self and study
- Emphasise non-judgemental position, discussion not a Q&A
- Assure confidentiality
- Check permission to use audio recorder
- Mobiles off
- Thank all the participants for attending, no right/wrong answers, views and experiences are what matter

2. **General background information**

Invite all of the participants around the room to introduce themselves (include profession, years working in haemophilia and where they work).

3. **Clinician views of the lived (patient) experience of having chronic joint pain**

- Medical management of joint bleeding (before current medical treatments)
- Pain management in this acute phase
- Do you believe this affects pain experience in adulthood
- How does it relate with their haemophilia diagnosis
    - Do you have a different approach to severity of disease
- How it affects their day to day life
- Do you know/ask how pain affects a person's work, study, family life
- Do you feel medical approaches have been helpful

(PROBE)

- Does it effect how active the patients are?
- How much? Why?
- Would you like to do more?
- What stops you?

4. **Methods of pain management being used**

- What current methods are they using
- What previously have they done
- Why did they choose these

(PROBE)

- Non medications such as illicit drug use, alcohol etc
- Did anything work well
- Why do they think it worked/ What did not work – why not
- Anyone else – GP?

5. **What is causing the pain**

- Why do you think people with haemophilia have pain

(PROBE)

-structural

-psychological/ mood/ expectation/ normal

- Have you noticed any particular things that happen to make the people you look after have/report more pain
- What is the relationship between these events and their pain
- Do you think 'pain' can be made easier/managed better

6. Using a rehabilitation intervention for joint pain in PWH

- what do you think about using exercise and activity to help pain
- Have you ever tried?
  - If – yes – how did it go?
  - If - no – why not?
- what do you think may happen if you were to encourage this in an individual with a painful joint(s)
- Would you have the confidence in a clinical environment to recommend rehab

(PROBE)

- Do you think this may influence your current management approach?
- Why do you think it would be ?bad
- have any of your patients been advised not to exercise – by who?- Why?
- Why do you think something like rehab may be a good approach?
- Do you think it may affect your patients approach to working or daily life?
- What things are important for you to know if you were to encourage a patient to take part in something like this

(PROBE)

- Education
- how long (how many weeks)
- What do you think of exercising as part of a group
- what kind of things you would be doing
- where it would take place (is that important)
- opinion of haemophilia Dr's – is that important
- Do you think it would be safe?
  - Bleed risk / more damage/ more pain

7. Barriers and facilitators to a planned intervention

- what is important for us to tell potential participants of a group such as this
- What things are important to help it run well
- Why do think people may not want to come

8. Outcomes to measures

We want to collect information about you before and after the intervention.

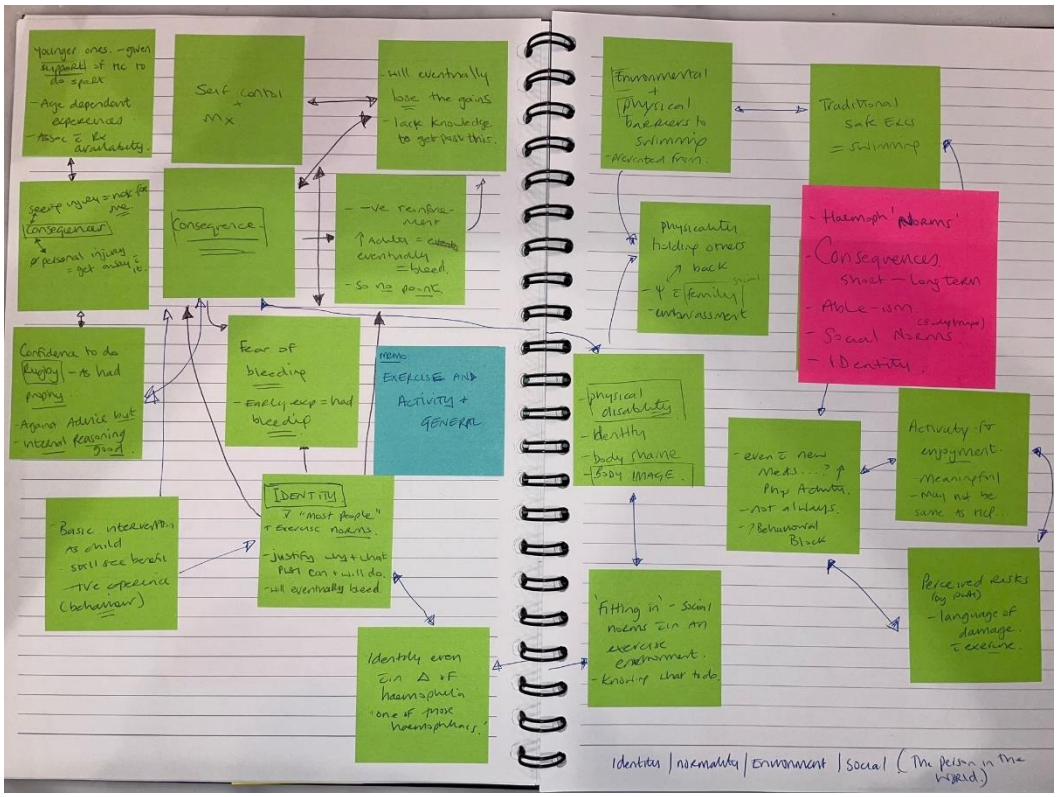
- What should we ask about to see if the group was helpful
- What matters most to you as clinician in trying to manage patient reported pain on a daily basis

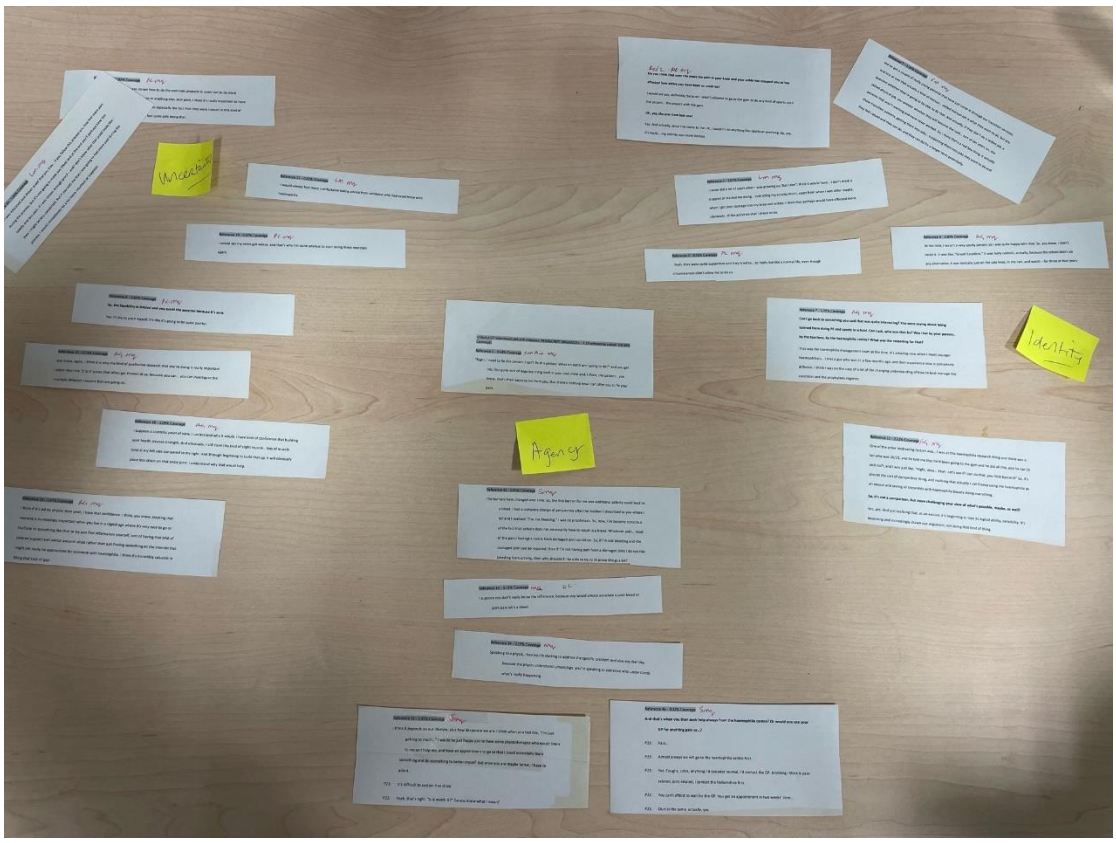
9. Anything else to add?

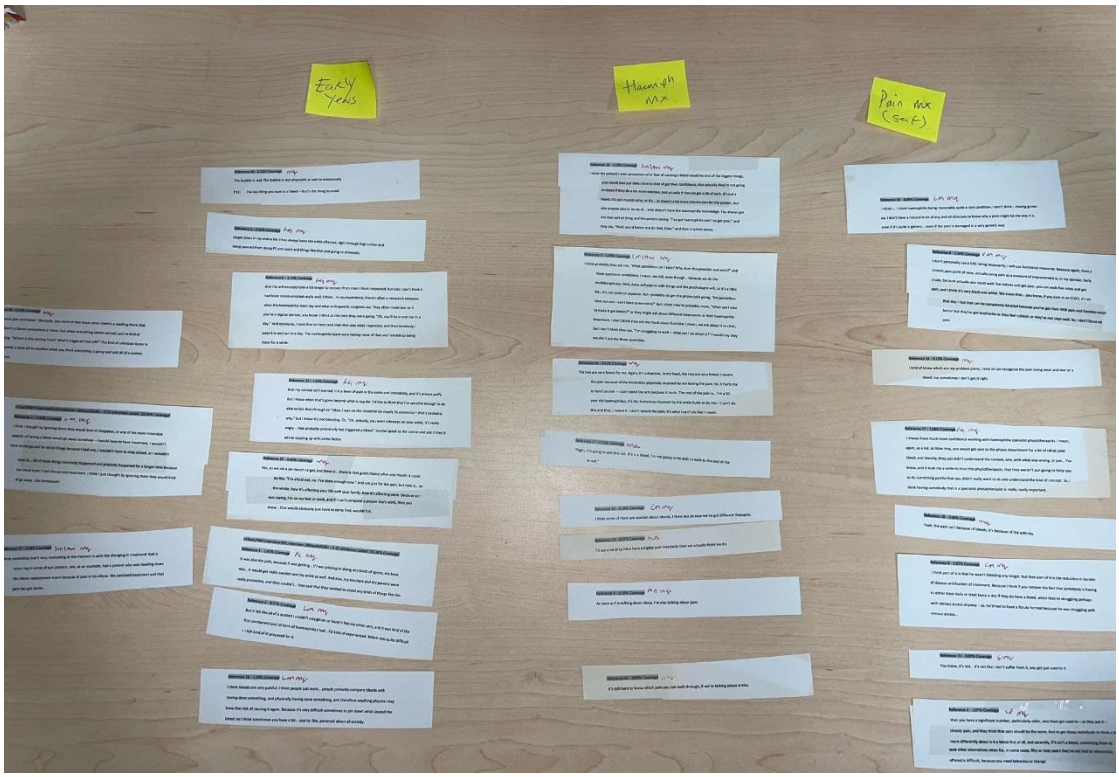
Have you any questions or thoughts to add about the things we have discussed here today?

10. Close the group/ Final thanks

Appendix J – Process of reflexive thematic analysis: codes and theme generation




Uncertainty
Identity
Agency


Early Years
Pain mx (Self)

Appendix K - Qualitative study publications – Chapter 5

DISABILITY AND REHABILITATION
https://doi.org/10.1080/09638288.2021.2018053

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

OPEN ACCESS Check for updates

How does a lifetime of painful experiences influence sensations and beliefs about pain in adults with severe haemophilia? A qualitative study

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ABSTRACT

Purpose: To explore the life experiences of pain in people with severe haemophilia and understand how such experiences influence beliefs and sensation of pain in adulthood.

Methods: A qualitative inquiry approach using focus groups and semi-structured individual interviews was used. Participants included people with severe haemophilia living with chronic pain. Data were analysed using reflexive thematic analysis.

Results: Fourteen men with a median age of 47 (range 23–73) agreed to take part. Eleven participated in two focus groups and three were interviewed over telephone. Two themes were conceptualised from the data: (i) haemophilia and pain – an evolving life biography (the personal narrative, historical, social, and medical context, continuous adaptation of activity choices, surveillance of pain and its meaning); (ii) *"My normal isn't normal"* – identity and self-agency (pain as a feature of life and identify with severe haemophilia, loss of enjoyable activities balanced against staying active, barriers to participation).

Conclusions: Pain is a constantly evolving, lifetime feature for many adults with haemophilia and it is viewed as part of their identity with their condition. Healthcare professionals working in haemophilia should try to better understand the influence of an individuals lived experience with their haemophilia on beliefs and behaviours of pain.

ARTICLE HISTORY
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KEYWORDS
Haemophilia; pain; qualitative research; experiences and beliefs; identity; reflexive thematic analysis

➤ IMPLICATIONS FOR REHABILITATION

- Severe haemophilia is a rare bleeding disorder that results in musculoskeletal joint disease.
- Adults with severe haemophilia have experienced multiple episodes of bleeding related musculoskeletal pain since childhood.
- Pain beliefs and behaviours in adulthood appear to be influenced by a lifetime of painful experiences associated with haemophilia.
- In order to better support people with haemophilia and chronic pain, healthcare professionals in haemophilia need to better understand how an individuals lived experience of pain helps inform their beliefs about it.

Introduction

Haemophilia A and B are rare X-linked congenital bleeding disorders, where normal circulating levels of clotting proteins (factors VIII and IX) that help maintain adequate haemostasis are significantly reduced or absent [1]. The World Federation of Hemophilia estimates a prevalence of 17.1/100 000 for haemophilia A and 3.8/100 000 for haemophilia B. Globally, it is expected that approximately 794 000 people have haemophilia, with 34% being severe (that is a factor VIII or IX level less than 1% of normal) [2]. In the UK, there are 8248 people registered with haemophilia, of which 2145 are severe [3].

Recurrent articular bleeding is a hallmark of haemophilia and is one of the most disabling features of the condition, with bleeding occurring early in the life of those affected, and continuing throughout the lifetime if the condition if left untreated [4]. Management of severe haemophilia involves regular intravenous replacement of the missing clotting factor or other more novel non-factor therapy to prevent spontaneous bleeding [5]. Haemophilic arthropathy is the consequence of repeated joint bleeding and is characterised by chronic synovitis and cartilage destruction, epiphyseal enlargement and bony deformity [6]. Many PWH over the age of 65 had no access to regular treatment until they were in adulthood, with those currently aged in their 40s having no access to effective treatment for the majority of their childhood. Consequently, many PWH have chronically painful, multi-joint haemophilic arthritis [7].

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Supplemental data for this article can be accessed here.

Pain is a cardinal sign of acute musculoskeletal bleeding episodes [8], whereas chronic pain associated with HA is now considered a significant clinical comorbidity. Pain is highly prevalent in PWH with data reporting acute pain being experienced by 20–68% [9,10] whilst chronic pain is present in between 30 and 71% of adults [10,11]. Whilst the basic science investigating pain mechanisms in PWH is lacking, it is generally accepted that both acute and chronic nociceptive input plays a large part in the pain experience in this population [12], with more recent data suggesting the possibility of neuropathic mechanisms in a smaller subset [13,14]. Intra-articular iron deposition following bleeding also initiates a pro-inflammatory effect on hypervascular and hypertrophied synovium [15]. The intra-articular processes of joint degeneration, capsular stiffening, and chronic inflammatory processes described in osteoarthritis [16,17] are likely very similar for PWH though yet to be fully investigated. Those PWH living with co-existing haemophilic arthropathy struggle to differentiate between pain associated with arthritic changes and acute onset joint pain which may or may not be associated with a bleeding episode [18]. This lack of specificity in perceived causal pain mechanisms is further complicated by wider medico-social, psychological, and cultural influences on the individual pain experience that accompany a rare inherited disorder such as haemophilia.

Bleeding and its management has been traditionally viewed within a model of biomedical intervention. Whilst this is appropriate within an acute bleed treatment episode or when engaging PWH in prophylaxis regimes to prevent bleeding, it struggles as a model of care provision to recognise the many competing experiences and influences which impact how an individual lives with their haemophilia. Pain associated with haemophilic arthropathy interferes with daily activity, mobility, work, and employment prospects [19,20]. PWH who have co-existing acute and chronic pain report a significant negative impact to their quality of life [21], which is made worse with multiple affected joints [22]. Recent UK NICE guidelines for chronic pain management encourage a more person centred approach [23] but there are limited accounts of the subjective exploration and attempts to understand the pain experiences of PWH. Knowledge and understanding of the life experiences of PWH in relation to haemophilia in their family, experiences of treatment and their own cultural and medico-social experiences may help enhance and inform approaches to pain management in the clinical context.

This study forms part of a larger project aiming to develop and test the feasibility of a rehabilitation based intervention as a component of a pain management approach for PWH. The development process sought to understand and explore the lived experience of pain in people with severe haemophilia, understand their beliefs around current pain management approaches and explore their views of exercise as a potential component of management, so as to inform and theoretically underpin a study protocol for a feasibility study. The current study aims to explore the life experiences of pain in people with severe haemophilia and understand how such experiences may influence their views and beliefs of pain now in adulthood.

Methodology

Study design

As the main aim of the study was to better understand the phenomena of pain experience in PWH, a qualitative approach using focus groups and semi-structured individual interviews was used.

With the focus of this study being the individual's subjective reality of their life experiences and beliefs of haemophilia and pain, it was underpinned within a relativist ontology, situated in an overlapping phenomenological and interpretivist epistemology. Within a constructionist paradigm, meaning from the social and cultural world is constructed and a better understanding of what it is like to live with haemophilia and chronic pain is gained.

Research team and reflexivity

The first author is a male clinical academic physiotherapist, 21 years qualified and with 15 years of experience of working in haemophilia, managing acute musculoskeletal bleed-related pain and observing the unique difficulties in managing chronic pain in this population. Beliefs about this study and approach were informed by the iterative development of the physiotherapy service over recent years in partnership with those PWH registered at the centre. Rigour and reflexivity throughout the study were maintained with regular research team meetings as well as a second author being present at the focus groups, and analysis and review of field notes and reflection. Analysis of data was discussed with the research team (one female nurse researcher, one female haematologist, two male academics, and one male person with haemophilia) and themes were discussed, modified reviewed and agreed.

Recruitment

Participants with were purposively selected from southeast and northwest England in order to achieve a variety of views and experiences. Inclusion criteria were those with a diagnosis of severe haemophilia A or B, who self-identified as having persistent pain associated with their haemophilia, i.e., the presence of haemophilic arthropathy diagnosed from clinical assessment, aged 18 or over and with an absence of any other condition that would be responsible for the presence of persisting musculoskeletal pain. Those who could not provide consent, those with mild or moderate haemophilia or had pain not associated with haemophilic arthropathy were excluded.

The study was promoted on social media platforms as well as using posters designed in conjunction with the UK Haemophilia Society (patient organisation). Those interested were encouraged to contact the lead author by phone or email to initiate further discussions to clarify any queries as well as check inclusion criteria.

Setting/location of groups

Two focus groups were held, in northwest and southeast England. Due to Covid-19 restrictions, telephone interviews were arranged in advance at the most convenient time for each individual participant.

Methods

The focus groups and interviews took place over a nine month period between June 2019 and March 2020. Written informed consent was taken on arrival on the day of the focus groups and by email on the day of the telephone interviews. The study was approved by the St. Georges University of London Research Ethics Committee (reference no. 2018.0309). The study was not registered.

The meeting opened with an agreement of the attendees to the ground rules of confidentiality and respect for others voice and opinion within the discussions. A topic guide was developed in advance for the focus group with input from the research team which also includes a person with haemophilia, and was used to inform all the research questions developed for the larger overall study (see Supplemental information). Questions were based on the overall aims and objectives of the study. Questions were open ended to encourage and enable free conversation and an opportunity to raise issues and topics of concern to those present. The topic guide for the interviews was based on the same guide as the focus groups, with small adjustments being made to question style in acknowledgment of the 1:1 approach. Probing questions and prompts were also used in the groups and interviews to gain deeper understanding of experiences and views being discussed. The approach was flexible enough to enable and engage with topics and discussions that were introduced by participants as relevant to them.

Each focus group had two moderators from the research team present. The lead author led discussions in the group whilst the second moderator provided support in observation of participants, made field notes, and helped draw in quieter participants to the discussions as necessary.

Focus groups and interviews were digitally recorded and transcribed verbatim.

Analysis

The analytic interest was focussed on the participants' personal experiences of haemophilia and pain and so an approach using reflexive thematic analysis (TA) was deemed appropriate. Broadly, TA seeks to identify and analyse patterns in data and is a shared approach across other analysis approaches such as interpretative phenomenological analysis and grounded theory. Reflexive TA acknowledges the importance of the researcher subjectively as an analytic resource as well as a resource for knowledge production [24]. This interpretivist approach views the researcher as never being truly separate from their own values and beliefs [25] and so places my ontological view as that of recognising multiple realities (relativist) within a subjective epistemology.

The six phase approach to reflexive TA was used here, and is viewed as a recursive, iterative process rather than a truly linear one. The phases are described as (1) familiarisation with data; (2) generating initial codes; (3) initial theme generation; (4) reviewing and developing themes; (5) refining, defining, and naming themes and (6) writing up [24,26]. Transcripts were initially read alongside the recording of the interview, first to check for accuracy of transcription and then again as a way to begin immersion in the data. The lead author led the analytic process of coding and theme development. Coding within reflexive TA is not a process for finding pre-conceptualised themes, but instead is fluid process integral to theme development [27].

The concept of data saturation was not used here as an end point to coding and theme development. Instead, and in keeping with reflexive TA approach, we did not identify codes/themes *a priori* to data analysis [28]. The inductive approach used here represents situated and contextual engagement and interpretation of data by the lead author rather than using consensus between coders (i.e., codebook approach).

Initial interpretations of codes, broad theme development and thoughts about the data's story were discussed with the other moderator who attended the group. As theme development became more solid, the wider research team discussed the findings leading to further refinement and analysis with codes being merged, removed, expanded and renamed as the data were further interrogated.

NVivo 12 Pro® was used was used to manage the dataset (transcripts and field notes).

Findings

A total of 14 people with haemophilia took part in this study. Sixteen people expressed an interest in taking part in the focus groups, but five were unable to attend on the specified date of the meeting. 11 PwH attended two focus groups (median age 52, range 28–73) and three were interviewed over the telephone (median age 28, range 23–30). Approximately, half of the participants were known to the lead author, as they were registered at the centre where he worked. Rather than bias, this familiarity was viewed as being beneficial to the process. Participants had a trusting relationship with the lead author, appreciating the need to be open and honest in the group/interviews and the importance of being able to share and discuss their experiences. The presence of a second moderator in the focus groups also ensured that reflexivity was strengthened in the analysis following. There were approximately 10 h of recorded interviews transcribed. Table 1 presents the demographic information of all those who participated. Pseudonyms are included for use in the narrative that follows. Two themes were conceptualised from the data: (1) haemophilia and pain – an evolving life biography and (2) "*My normal isn't normal*" – identify and self-agency.

Theme 1: haemophilia and pain – an evolving life biography

Here the medical, historical, and social evolution of life with haemophilia is explored, particularly relating to living with a rare disorder and the pain associated with it.

The historical narrative of haemophilia. For older men with haemophilia, early life experience with medical care of haemophilia is primarily reflective on a lack of any medical treatment and limited awareness of haemophilia. Significant periods of hospitalised immobilisation was normal, and invariably ended up provoking further bleeding. In early years a lack of treatment and expertise from both parents and the medical profession meant that being cared for was viewed as "*damage limitation*" *(Hugh, 65)*. For almost all older participants, "excruciating" pain from bleeding was a repeated and common experience of growing up with haemophilia:

Table 1. Participant demographics (pseudonyms) – people with haemophilia.

	Pseudonym	Age	Diagnosis	UK/non-UK born	Employment	Prophylaxis
1	Tony	55	SHA	Non	Y	Yes
2	Adam	28	SHA	UK	N	Yes
3	John	42	SHA	UK	Y	Yes
4	Jack	57	SHA	UK	N	Yes
5	Greg	39	SHB	UK	Y	Yes
6	Will	52	SHA	Non	N	Yes
7	Ivan	73	SHB	UK	Retired	Yes
8	Alex	58	SHA	UK	Retired	Yes
9	Owen	52	SHA	Non	Y	Yes
10	Andy	40	SHA	UK	Retired	Yes
11	Hugh	65	SHA Inhibitor	Non	Y	Yes
12	Sean	23	SHA	Non	Student	Yes
13	Leon	28	SHB Inhib	UK	Y	Yes
14	Nick	30	SHA	UK	Y	Yes

SHA: severe hemophilia A; SHB: severe haemophilia B; Inhibitor: (presence of antibodies that prevent factor replacement treatment from working effectively).

> I remember one incident where I was on admission and I had multiple anal inserts, and unfortunately once you get one in they can't give you another for a couple more hours. At the end of the day, they had to resort to morphine shots to calm me down, and even that couldn't keep me calm for, like, 15 to 20 minutes before the pain starts to shoot through the roof again. (Andy, 40)

Localised non-specialist medical care and potentially dangerous or ineffective interventions for pain relief were the norm until development of, and access to effective medical treatment revolutionised acute bleed management.

> This must have been in the early '60s, I think – they gave me one of the first experimental doses of the factor IX concentrate, and that worked. And I thought, "WOW!" … Because that fairly quickly stopped the bleed and the pain went down. (Ivan, 73)

As care advanced from hospital based treatment to clotting factor concentrates administered independently at home, people with haemophilia began to see positive enhancements to their life and activity. The relationship between the symptom of pain and the possibility of that pain being a bleed is complex and has evolved over time and with age, experience of treatment improvements and treatment availability. However, the advent of effective prophylaxis and diminishing episodes of spontaneous bleeds is challenging the internal reasoning and decision making processes that uses pain as a marker for bleeding-

> I suppose you don't really know the difference, because you would always associate a joint bleed or joint pain with a bleed. (Adam, 28)

Haemophilia, pain, and the family. The diagnosis of haemophilia within a family was for some parents a catastrophic disruption to life. A child with haemophilia meant that they were required to blindly navigate imperfect medical care as well as trying to provide the best parental care and protection they could, at a time when knowledge and medical provision were scarce:

> … diagnosed at six weeks old – I think, from memory – it came as a complete shock to my parents. They'd never heard of haemophilia or how to cope with it, or how to manage me. I was their son. I was in incredible pain a lot of the time. (Ivan, 73)

Living with haemophilia and the bleeding episodes was disruptive to family life, familial roles, and relationships. The child with haemophilia brought with it responsibilities and need for management that was more than what would be seen normally within most families at the time. Anxiety of having to disclose a bleed to a parent for fear of an angry response, resulted in many hours of no treatment and increasing pain:

> And my dad was like really strict, so what I'd do is, if I hurt myself, I'd try and treat myself, like get… like try and… "Oh God, I've got to tell him, I've got to tell him." And then the ambulance would come, like half eleven at night, and I'd make it worse, and I'd have to be in hospital. (Jack, 57)

Pain associated with haemophilia was an ever present and normalised feature within the family unit whilst growing up. How participants experienced, reported, and behaved with pain has evolved into their adult lives, continuing to be a feature in their own families now. Some feel that their pain is a personal experience not to be shared or discussed with their partners or family, whilst others describe teaching vigilance of their pain to their children:

> If it's a bad day, I will try and keep my son aware to some degree, so that he can understand if I'm snappy it's not because of something he's done. It's difficult because he's only eight… he knows his dad has issues in certain areas. (Will 52)

Fear, consequence, and adaptation. The worry pain may be a possible sign of bleeding permeates all cognitive processes, behaviours, and activity choices in the lives of men with severe haemophilia –*'The last thing you want is a bleed – that's the thing to avoid.' (Tony, 55)* Whilst pain is unpleasant, it is an experience that is accepted as almost always being present and is to a degree, accommodated and moderated. Bleeding, although intermittent, is unpredictable and has greater consequences on immediate and future physical ability and social interactions.

> I'm just sort of thinking, at the back of my mind I'm hearing pain is like half an inch away from… not a bleed, but disaster. You know, because you might not just have a bleed – like a bad knee, a bad arm or something. I've been hospitalised with a psoas bleed and I was lucky to stand up straight after that. (Hugh, 65)

The fear of bleeding has lessened with being on prophylaxis. Fear and anxiety as a response is still manifest, but more in relation to the consequences of their lifetime of haemophilia on their physical, social, and psychological being. Worry about bleeding merges with the constant stress of monitoring the state of their joint on a daily basis:

> …with the joint pain for me: there's a degree of unpredictability. Some days you can just push through and yes, you may be sore the next morning, but you will be okay. And other days, you're going to be in a lot of pain that night. (Will, 52)

Haemophilia and its physical side effects is viewed as something that prevents an acceptable, predictable continuity of life. The need for a structural cause to attribute to pain is coherent with a biomedical model of health and well-being that has been a feature of the medical care approach and life with haemophilia. The presence of pain independent of bleeding or injury is a difficult concept for many to contend with, presenting a challenge in what to do, embedding doubt and the possibility of negative consequence and inhibiting physical activity even more:

> You're constantly in a protective mode, aren't you, really. (Tony, 55)

Theme 2: "My normal isn't normal" – identity and self-agency

Here, we present how the sense of physical self, both that observed by others and the internalised perception of bodily and social identity because of haemophilia has, and continues to be, influenced by internal and external factors.

Physicality and ableism. The bodily and perceptual changes acquired because of haemophilia start in early age. The internal sense of physical self exists alongside ongoing salience for bleeding, alongside comparison of themselves against unaffected peers. Reflection and reminiscence of being younger and what was *"their best years" (Andy, 40)* is common, often related to feelings of having been more active and having less pain, but viewed now as a loss because such enjoyment with activity is fleeting and unlikely to be achieved with their current physical state. Whilst the loss is mourned it is also described in terms of inevitability in having to make decisions to stop enjoyable physical activities as *"it was more important to be fit and able to go to college the next day, or to go to my workplace, or got to my Saturday job" (John, 42)* than risk bleeding and more pain.

Men with haemophilia appear to want to be able to do more despite their physical limitations. They want support to do so, acknowledging the difficulties are physical, practical, and psychological because getting older with affected joints is hard and

brings with it other issues of physicality and *"there's no point in living longer if you're in a mess" (Hugh, 65).*

Even with support, issues with body image and environments that do not accommodate disability impair physical activity and so trying to be physically active becomes more difficult:

> You see, I enjoyed swimming, but then I had trouble getting out of the pool. And then there's the embarrassment factor … trying to get out of the pool. So the arm is bent, I can't push myself up, and then trying to get out up the steps, I'd hold the steps but I'd have to make sure I've got my feet planted just right so I can pull up on that. (John, 42)

Difference and sameness. Perceptions of identity in PWH are complex, existing in the social setting as well as implicit in their search for comparators to them and normalcy in day to day life. Exposure to such views happens early on at school, with their differences and social capital being negatively influenced by others in positions of authority-

> I remember, the first day of secondary school, I was brought up in front of assembly, in front of 300 kids, and pointed at, and they said, "Don't touch this guy." The first day of my first year at secondary school, they said, "Can Jack please come to the front, please." The first day at this new school. "This boy, he's delicate and he bleeds." (Jack, 57)

Whilst some avoided social contact that carried any risk of bleeding or injury, others were removed from school entirely to be home schooled, further highlighting their difference. There is a complex relationship with past experiences and how it influences social identity with haemophilia, to the point where it has negatively influenced behaviours that could have been of benefit:

> I live in a really big student town. I joined [the gym] in July or August and all the students were away and it was marvellous. It was great … having that kind of window of opportunity to go and explore and begin to feel comfortable and use the machines and just having a play around, particularly having never felt like I belonged in those kinds of spaces, was really useful. (Nick, 30)

As well as social identity perceptions there appears to exist a multilayered view of identity specific to haemophilia itself. Acceptance of the condition and its effects by both HCP's and broader society is important, as being a person with haemophilia in itself is not how these men want to be defined, although there is acceptance that as a group *"the legacy is we have been damaged"* (Hugh, 65).

Upward comparison to those perceived as normal appears to help strengthen their own perception of self with haemophilia, particularly in regards to pain its intensity and their ability to cope with it, and the view that PWH have *"experienced real pain" (Owen, 52).*

There is a downward comparison made also, in that those without haemophilia who have poor surgical recovery, for example, just did not work hard enough. This appears to relate to a perception that PWH have developed a better fight to work harder to recover, because they have had to do it so many times. Pain is as much part of the identity of a PWH as having haemophilia. Pain is normal and life experiences embed the acceptance of pain within their view of themselves.

Whilst examples of upward and downward comparison appeared to be used to strengthen self-perceptions, comparing self with other PWH raised more uncertainty and questions about their own views and behaviours. There is judgement and disbelief about those with haemophilia who can participate in elite sporting activity – *"We've got an extremist in our membership – Alex Dowsett" (Owen, 52).* In a modern era of better haemophilia treatments, there appears to be a constant challenge to their view of themselves leading to questions about if they should and are able to do more. Individual fears about pain and possible negative effects are confronted and challenged by seeing and hearing about others with haemophilia having some positive outcomes with activities such as exercise, further challenging perceptions of identity.

Discussion

The aim of this study was to investigate and explore the life experiences of pain in PWH and to understand how such experiences may influence their beliefs and sensations of pain now in adulthood. The account presented here highlights that pain for PWH is a lifelong, continually evolving experience that has been deeply influenced by social, cultural, and medical experiences within that lifetime. It is this novel qualitative exploration and explication of the multifactorial influences on pain in PWH that provides findings of potential clinical relevance.

To contextualise an understanding of the pain experience in PWH, it is important to understand the historicity of such experiences within a timeline of medical treatment. Up to the 1950s/60's management of acute musculoskeletal bleeding was limited to bed rest and access to transfusions of whole blood or fresh frozen plasma [29]. This treatment was scarce, came with a substantial treatment burden and discomfort, and was only prescribed if the doctor deemed the bleed severe enough, which meant many PWH avoided it by staying at home and tolerating the pain of bleeding. Pain associated with acute bleeding was seen as something to be managed in co-ordination with bleed management and resolution, particularly with the development of effective treatment in the 1970s, whilst chronic pain presented "considerable therapeutic difficulty" [30] with advanced haemophilic arthropathy management viewed as a palliative endeavour [31].

The consequences of childhood pain on parental emotions are also challenging, and those in this study were all very aware from a young age how their condition affected their family. Managing unpredictable challenges such as bleeding and pain for mothers of boys with haemophilia was beset with distress [32]. Similarly, parents of children with Juvenile Idiopathic Arthritis report desperation in trying to manage painful episodes associated with the illness and the physical and emotionally draining effect on the entire family and family life being affected [33]. The fear of a child being in pain and the ever present feeling of potential danger traps parents in a "cage of fear", resulting in an ingrained behaviour of always thinking about possible consequences [34]. The constant surveillance for pain and danger is not only confined to parents. Young people with sickle cell disease report that they are always monitoring for signs of sickle crisis and pain so as to be ready to take action with it, but are mindful as to when and who to disclose it to so as not to be marked out as different or disrupt their life [35]. Such a view meant that non-critical sickle pain was often managed at home outside of any clinical context [36]. Palermo and Chambers [37] proposed an integrated model of factors relating to a child's pain within the family. It highlights the reciprocal influence of pain itself on relationships, parenting styles/behaviours and family functioning and that such factors are not fixed as they depend on the age developmental stage of the child. Such a model helps contextualise the almost constant requirement of parents of children with haemophilia in trying to manage recurrent painful bleeds in an era of limited medical treatment. It is notable that there are similarities in this parental behaviour seen now in adults with haemophilia. Whilst they contemplate their pain and the ever present fear of bleeding, how they choose (or not) to communicate about their pain also

impacts on their own family as they try and manage their perceived burden of themselves on others.

Physical activity, due to its associated risks with bleeding, was curtailed in the formative years of many PWH. Whilst this imposed difference was unwelcome and stigmatising, many PWH still feel guilt that their own actions at the time have added to their current experience of pain and functional difficulties [38]. Rolstad [39] found in their qualitative study that older men with haemophilia carry a psychological burden that is influenced by the degree of social stigma and ignorance they encountered in their formative years. Whilst the cohort in this study are able to recount negative experiences of their life and pain associated with their haemophilia, it appears to be situated within a coherent, reasoned and somewhat positive account of that life – and one which makes sense to them and others with shared experiences. This is perhaps an extension of the coping strategies developed in childhood but it may reflect acceptance of what is felt to be currently realistic. A large ethnographic study of PWH in five countries, highlighted that although there is a trade off with pain and the need to stay active, there is a view for many that things used to be worse and that this perhaps prevents many from being able to live their fullest life possible. This lived experience of what was, alongside their individually appraised experiences of everyday life continue to influence how pain, function and activity exist within a desire to avoid bleed provocation at all costs [40].

Whilst living with a rare congenital condition can bring with it a burden of disease management, for many people they do not wish to be defined by that condition. Similar to findings by described by Kalmar et al. [41], participants in this study spoke with clarity on how their haemophilia does not define them and that living with haemophilia is their "normal" – for it is all they have ever known. The need for an illness or condition to not dominate life is highlighted in other conditions such as sickle cell disease, where individually perceived normalcy is constructed apart from the disease itself [42]. Likewise, the ability to accept and live with pain as they do was associated with the belief that PWH live with an enhanced pain tolerance due to their many previous experiences of pain, a finding also reported previously by others [43,44]. It is the association and identity of having pain alongside their haemophilia that is a notable exception in this study. Our data suggest that for many PWH their identity as a person with chronic pain is as much a part of their identity as haemophilia is. Whilst some broad similarities were found in our data, many of the men interviewed here appeared to be accepting of what they were able to do with their pain being present and they had altered their lifestyle accordingly. It is unclear if this is particular to this group of men included in this study, or perhaps a wider indication of access to both haemophilia treatment and experienced healthcare teams.

Understanding the individual, lived perspective of a PWH experiencing multiple painful events provides a better way of understanding their acute and chronic pain. It is the embodied relation between the person and their environment that helps shape the many different ways pain can be experienced [45], and therefore requires more than a unimodal biomedical approach. Acute pain (such as that in an acute bleed) captures attention by interrupting activity, demanding a response so as to protect the body part (as necessary), as well as creating a motivational context in which to do something (such as rest or take treatment in the case of bleed). The experience of chronic pain (as with joint arthropathy) continues to interfere with activities and the sense of self, and requires accommodation to the ongoing pain if a person is to define who they want to become with that pain [46]. The companion study to the one described here identified the limitations with current pain management approaches that PWH have experienced and highlights the uncertainties with unimodal pain management approaches such as exercise [47]. Whilst acknowledging local anatomical and higher cortical physiological responses to acute and chronic pain, we believe this current study provides much needed contextual insight in respect of possible contributing factors to the pain experience for people with severe haemophilia.

Despite the strengths of this study, there are acknowledged limitations. All of the participants included in this study were resident in the UK and therefore receiving what would be considered world leading haemophilia care. We acknowledge that those PWH in low resourced countries and in healthcare systems with limited or no access to effective haemophilia treatment may not have the same experiences or beliefs expressed by those included here. A strength, however, is that some of our participants did not grow up in the UK and so were able to express and discuss their experience of pain from that perspective. Further research should be mindful of the socio-economic and cultural influences of healthcare on the individual experience of pain in PWH.

This study only included people with severe haemophilia. This is in no way to diminish the experiences of those with moderate or mild haemophilia, but it remains that those with severe haemophilia remain most likely to experience more episodes of bleeding and painful joint damage from a young age. It is imperative therefore to understand these experiences. Further research should seek to explore if people with moderate and mild haemophilia have similar or differing life experiences of pain as well as thoughts and beliefs relating to pain.

A researcher led, reflexive TA approach rather than that of codebook approach to coding was employed here. This may mean other researchers who would come to analyse this dataset with a different philosophical position or clinical experience may come to different conclusions. This in itself is not a limitation but we present the positionality of the authors in the study and acknowledge that it is the unique clinical and academic experience of the lead author that enables the depth of analysis presented here.

Conclusions

Pain is a well-established feature of acute bleeding in haemophilia. This study highlights that early experiences of bleeding and persistent pain associated with joint arthropathy may play a role in how pain becomes embedded in the life experience of living with haemophilia. Continuing to view pain as a wholly biomedical construct fails to appreciate and understand the effect of multiple unique pain experiences that PWH live with. Healthcare professionals in haemophilia should be mindful of the individual's lifetime experience of pain in clinical encounters and seek to understand its relevance to practice and any interventions that may be required.

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The experiences and beliefs of people with severe haemophilia and healthcare professionals on pain management, and their views of using exercise as an aspect of intervention: a qualitative study

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ABSTRACT

Purpose: To explore the experiences, views and beliefs of people with severe haemophilia and healthcare professionals (HCPs) on approaches for pain management, as well as their views on exercise being used as an aspect of management.

Methods: Taking a qualitative inquiry approach using focus groups and semi-structured interviews, participants included people with severe haemophilia living with chronic pain and haemophilia HCPs. Data were analysed using reflexive thematic analysis.

Results: Fourteen men with haemophilia with a median age of 47 (range 23–73) and six haemophilia HCPs agreed to participate. Of the people with haemophilia, 11 attended two focus groups and three were interviewed over telephone. Healthcare professionals were interviewed face-to-face. Two themes were conceptualised from the data: (i) haemophilia management and pain management is discordant (imbalance between good haemophilia care but poor pain management, historical medico-social influences on pain management, the need for trust); (ii) uncertain about exercise but clear on what matters (conflicting views on exercise, the need for proof of safety, personalised care).

Conclusions: Options for effective pain management remain limited and what is used is heavily influenced by beliefs and experience. Exercise as a treatment option in pain management is conceptually acceptable for people with haemophilia. Effective pain management requires understanding of individual beliefs and fears, and a personalised approach supported by knowledgeable, trusted clinicians.

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➤ IMPLICATIONS FOR REHABILITATION

- Musculoskeletal joint pain and its relationship with bleeding in people with haemophilia continues to be a management challenge.
- Current pain management strategies are of limited effectiveness with little evidence of an approach that reflects the multi-modal pain experience.
- Whilst exercise and rehabilitation approaches are conceptually possible for people with severe haemophilia, barriers remain regarding perception of overall safety and effectiveness.
- People with severe haemophilia may consider exercise as part of a pain management strategy if it is individualised, and they are supported to do it by clinicians who understand them and their haemophilia.

Introduction

Haemophilia is a rare congenital bleeding disorder characterised by a deficiency in circulating levels of clotting factor proteins VIII (haemophilia A) or IX (haemophilia B) [1]. The presence of adequate factor VIII and IX is central to the process of normal blood coagulation, enabling the generation of sufficient thrombin to stop bleeding and permit adequate healing to take place. In its untreated state, spontaneous bleeding into the muscle and synovial joints is the hallmark of severe haemophilia, with most children with severe haemophilia having their first bleed by the age of 4 years old [2].

Articular bleeding mainly affects the ankles, knees, and elbows, and over time the repeated exposure to blood products has a deleterious effect on the articular cartilage and bone health. Haemophilic arthropathy (HA) is the term given to this process and is characterised by bony deformity, cystic change, cartilage destruction, and pain [3]. For almost all people with severe and some with moderate haemophilia, current management is

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Supplemental data for this article can be accessed here.

predominantly intravenous infusions of recombinant clotting factor proteins. This is done regularly at home to prevent bleeding occurring and is termed prophylaxis. For those with mild disease, and others who choose not to do "prophylaxis", factor replacement is administered after a bleed has happened, known as "on-demand" treatment [4].

Chronic pain associated with the presence of HA is a significant comorbidity of haemophilia with figures suggesting between 20 and 68% of people with haemophilia are affected (PWH) [5,6]. Whilst there has been little in the way of research investigating pain mechanisms in PWH, it is widely assumed that similarly to osteoarthritis, acute and chronic nociception is the main mechanism [7,8]. However, there is growing awareness of the likely multifactorial influences on an individual's pain experience whereby some PWH with no arthropathy report ongoing pain [9], as well the presence of pain in PWH not correlating with degree of joint damage and being a poor indicator of functional ability [10]. That said, PWH who are older and with a greater amount of joints affected by HA experience significantly more pain [11,12] and worse levels of psychosocial distress that negatively affect quality of life, mental well-being, function, and employment [13–15].

Despite the scale of the problem, there remains little in the way of published guidance for effective management of chronic arthropathic joint pain in PWH. Between 21 and 50% of PWH feel that their pain is poorly managed by healthcare teams [6,13] and this likely accounts, in part, for the wide range of strategies for pain management reported by PWH. Surveys in PWH have highlighted additional clotting factor treatment, opioids and non-steroidal anti-inflammatories, as well as rest, ice, compression, and elevation remain the most widely used methods for both acute and chronic pain [5,16], with other approaches including prayer, relaxation, deep breathing, and swimming also being used [17,18]. Whilst some have recently stated the importance of multi-professional expertise for pain management in PWH [19], psychology, physiotherapy, or exercise based strategies are seldom reported as being used by PWH [11,17].

The evidence base for effective and cohesive pain management approaches in PWH is lacking. NSAID's and in particular COX-2 inhibitors, have shown more positive effect on reducing pain intensity than acetaminophen in those PWH who have HA [20,21], but worries remain about potential bleed risk if used for an extended time [22]. A psychologically based approach using an educational DVD that sought to influence self-efficacy in managing pain demonstrated shifting participants from a pre-contemplative to contemplative state of readiness to change [23]. Another small pilot study using hypnosis showed some positive, but not significant improvement effect on pain interference and quality of life [24] Whilst exercise in general appears safe to do with PWH [25], a recent systematic review found that there is low level evidence of effectiveness of many physiotherapy interventions (exercise, manual therapy, electrotherapeutic agents) on pain and functional outcomes [26]. A recent study implementing a combined intensive physiotherapy/occupational therapy intervention of strength and balance exercises, group work and education and rehabilitative approaches to activities of daily living was unable to show any significant improvements in pain or quality of life [27]. To the authors' knowledge, there remains no published study that acknowledges or evaluates a multi-disciplinary approach to chronic pain management in PWH. Whilst some authors have identified fear of bleeding and further pain as barriers to being more active with haemophilia [28], there remains relatively little understanding of the lived experience of PWH and how they manage their pain, as well as the experiences of the HCPs who look after them. Insight into perspectives, thoughts and behaviours towards chronic pain from both parties is much needed if clinical care and individual approaches to pain management are to improve.

This study is part of a larger, ongoing research project that aims to develop and test the safety and acceptability of an exercise-based rehabilitation intervention for PWH who have chronic pain. Whilst it is acknowledged that the success of any pain management approach will likely require many individualised components, of which exercise may be one, the lack of quality research into the component parts requires an approach such as this to inform protocol development. A companion paper to this one explored how of a lifetime of painful experiences influenced beliefs about pain in adulthood in people with severe haemophilia [29]. The aim of the current study was to explore the experiences, views, and beliefs of PWH and haemophilia healthcare professionals (HCPs) around pain management strategies, and further investigate their views about exercise as a possible component in a pain management approach.

Methodology

Study design

As this was an explorative study seeking to better understand views and beliefs around pain and its management from PWH and haemophilia HCP's, a qualitative approach using focus groups and semi-structured interviews was used. Focus groups bring together a group of people in order to discuss and share their own views and experiences around a particular topic, whilst semi-structured allow participants to speak freely and provide their own valid account around the topic at hand [30].

Whilst those in the research team working in haemophilia have long observed the complexities and difficulties in the management of chronic pain in this population, we acknowledge that approaches have been empirical at best, with varying degrees of success. There is an urgency in understanding the need to attempt to contextualise healthcare approaches to pain with the experience of the PWH receiving that care. As we were seeking to understand each participants own subjective reality about pain management and their views and beliefs about exercise, a relativist position with an interpretivist and phenomenological epistemology was taken. As no predetermined theories or frameworks were used, an inductive approach to analysis was used.

Research team and reflexivity

The research team comprises the lead author who is a male clinical academic physiotherapist with extensive experience of working in haemophilia (15 years), a female nurse researcher with extensive experience in haemophilia, a male professor of rehabilitation science with an interest in pain management in arthritis, a male clinical academic physiotherapist specialising in haemophilia and a female professor of haematology. Regular meetings and supervision throughout this process helped ensure rigour and reflexivity was maintained.

Recruitment

The study was advertised on social media and on posters that were displayed in haemophilia centres in south-east and north-west England. For those people with haemophilia, inclusion criteria were a diagnosis of severe haemophilia A or B, who self-identified as having persistent pain associated with their haemophilia,

i.e., the presence of HA, aged 18 or over and with an absence of any other condition that would be responsible for the presence of persisting musculoskeletal pain. As the HCP's most likely to have first-hand experience of pain in PWH, an invitation to participate email was sent via the professional clinical interest groups of haematologists, physiotherapists, nurses, and psychological professionals working in haemophilia in the UK. Inclusion criteria for the HCPs were the requirement to have experience in working clinically with PWH in adult haemophilia centres. All participants had to be able to communicate in spoken English. Those interested were encouraged to contact the lead author by phone or email to initiate further discussions to clarify any queries as well as check inclusion criteria.

Setting/location

All interviews are focus groups were conducted between June 2019 and March 2020. Two face-to-face focus groups were held for PWH in south-east and north-west England. Due to Covid-19 restrictions, interviews with PWH were conducted over the telephone at a mutually convenient time agreed in advance with participants.

Although a focus group was planned for HCPs, meeting logistics agreeable to all who expressed an interest were not forthcoming, so it was decided to proceed with semi-structured face-to-face interviews instead. Interviews were arranged at times and places most suitable to the interviewee.

Methods

Written informed consent was taken on arrival at the focus groups and face-to-face interviews and over email on the day of the telephone interviews. The study was approved by the St. Georges University of London Research Ethics committee (reference no. 2018.0309). The study was not pre-registered.

Topic guides were used for the PWH focus group, PWH interviews and HCP interviews based on the overall aims of the study (see Supplemental information). Developed in partnership with a person with haemophilia, they were informed by the current research literature in the area, clinical experience, and the research question at hand. Questions were open ended allowing naturalistic responses. Two moderators were present at the focus groups with one (the lead author) leading the group discussions and a second providing support in participant observation, making field notes and aiding those noted to be quieter to be drawn into conversations.

Both focus groups and all the interviews were digitally audio recorded and transcribed verbatim.

Analysis

In keeping with the explorative nature of the study and with the intended focus on the subjective and sense making experience of pain management, an analytic approach using reflexive thematic analysis (RTA) was justified.

The key defining feature of RTA a compared to a coding reliability or codebook approach is that the codes and resultant themes are created at the intersection of the data itself, the analytic process and subjectivity [31]. Knowledge is produced with the researcher being acknowledged as an analytic resource [32]. RTA is described as a six phase recursive approach comprising (1) familiarisation with the data, (2) coding, (3) generating initial themes, (4) reviewing and developing themes, (5) refining, defining, and naming themes, and (6) writing up [33,34]. The lead author conducted the data analysis. Following familiarisation through immersion in the data, initial coding across both semantic and latent interpretations enabled initial theme development. As RTA is not a linear process, further refinement occurred as analysis developed, within and across each transcript dataset, moving backwards and forward through the stages.

A priori codes were not used to inform analytic approaches; therefore, the concept of data saturation was not used as it is incompatible with RTA as a researcher led, theoretically informed interpretive practice. The lead and last author discussed the data findings as initial coding led to theme development. The other members of the team were involved in iterative discussions to further refine the analysis findings as the final theme structure came to be constructed. All transcripts and other datasets such as fieldnotes were managed using NVivo 12 Pro®.

Findings

A total of 14 PWH and six HCPs took part in this study. Of the 16 people who expressed an interest in attending the focus group, 11 PWH attended two focus groups due to availability on the day. After a second call for volunteers under the age of 30, and due to Covid-19 restrictions, three PWH were interviewed over the telephone. The HCPs were all interviewed face-to-face. The first focus group ran for 130 min, and the second for 180 min. The average interview length for PWH was 40 min (27–48 min) and 55 min (48–63 min) for HCP's. Just over half of the haemophilia participants were known previously to the lead author as they attended the centre where he works. This familiarity was viewed as having a positive effect as it encouraged open and honest participation in the process, and participants felt safe and secure in the anonymity of their responses. There were approximately 15 h of recorded interviews transcribed.

The six HCPs included physiotherapists ($n = 2$), a haemophilia nurse ($n = 1$), haematologists ($n = 2$), and a psychology professional ($n = 1$), with an average of 12.5 years working in haemophilia (range 4–20 years). Table 1 presents the demographic information of the PWH who participated. Pseudonyms are included for use in the narrative that follows. Two themes were conceptualised from the data: (1) haemophilia management and pain management is discordant; (2) uncertain about exercise but clear on what matters. The subthemes within each theme are described in the text below.

Table 1. Participant demographics (pseudonyms) – people with haemophilia.

	Pseudonym	Age	Diagnosis	UK/non-UK born	Employment	Prophylaxis
1	Tony	55	SHA	Non	Y	Yes
2	Adam	28	SHA	UK	N	Yes
3	John	42	SHA	UK	Y	Yes
4	Jack	57	SHA	UK	N	Yes
5	Greg	39	SHB	UK	Y	Yes
6	Will	52	SHA	Non	N	Yes
7	Ivan	73	SHB	UK	Retired	Yes
8	Alex	58	SHA	UK	Retired	Yes
9	Owen	52	SHA	Non	Y	Yes
10	Andy	40	SHA	UK	Retired	Yes
11	Hugh	65	SHA inhibitor	Non	Y	Yes
12	Sean	23	SHA	Non	Student	Yes
13	Leon	28	SHB inhibitor	UK	Y	Yes
14	Nick	30	SHA	UK	Y	Yes

SHA: severe hemophilia A; SHB: severe haemophilia B; inhibitor: presence of antibodies that prevent factor replacement treatment from working effectively.

Haemophilia management and pain management is discordant

Here, the assessment and management of pain, even as an acknowledged co-morbid aspect of life with haemophilia, is viewed as being less effective than haemophilia medical care, even though trust in the specialist healthcare team is high.

Experience, knowledge, and understanding of pain

From an early age, PWH and their families have been conditioned to use pain as a marker to evaluate/diagnose bleeding so as to initiate a management strategy. The "if in doubt, treat" mantra was there to initiate clotting factor therapy as soon as possible to lessen bleed damage. The clinical language of possible danger was matched with behaviour of rest, subservience and waiting for resolution, but in adulthood and in an era of less bleeding, this behaviour is less than useful.

> I think their go-to is, "This is a bleed," and I actually think there's quite a lot of undermanagement from MSK [services], because everything is put down to a bleed. (Rose, physiotherapist)

The reality that pain may exist without bleeding requires some form of acceptance internally but is not necessarily accompanied by a suitable solution, and so a newer developing form of interoception is required for those living or experiencing pain whilst on prophylaxis:

> I was stuck in bed for a couple of… and it wasn't getting any better. And I was thinking it was a bleed, but it wasn't – it was tendonitis. (Jack, 57)

Whereas PWH have their own individual life story which feeds and moulds the narrative of their life lived with haemophilia, HCPs rely on the experience of hearing and seeing those living that life to build a picture of trying to understand what that must be like. PWH tend towards a biomechanical/biomedical basis for pain being present such as environmental provocations (walking on cobblestones), prolonged weight-bearing activity or bleeding. HCPs acknowledge these patient-reported "reasons" but hear and incorporate them into their own reasoning model, helping better understand observed patient behaviours:

> I could see potentially how patients are self-diagnosing bleeds as a way of coming to terms or having a reason for their pain. And actually, if you're ringing up work saying, "I can't make it in today because I've had a bleed," that's quite different to, "I can't come in today because my pain is too bad." One is quite sort of acceptable and one is…. (Rose, physiotherapist)

Care models and healthcare provision

A conflict appears to exist between PWH and HCP's in how pain is managed. HCPs appear to be accepting of the fact that patients are not talking to them about pain because they talk about other profession specific issues (e.g., medications with the doctor), whereas PWH believe that they are being asked generic tick box questions:

> The doctors, I'm getting "Are you taking your Celebrex? Are you taking your factor? Sorry you're in pain". And that's where the conversation kind of ends, and you get fobbed off to the physiotherapist. (Will, 52)

Assessment of pain is challenging. PWH perceive that the value of pain rating or scoring scales is low and only helpful for clinicians.

> I struggle with the 1 to 10 thing. Because, I mean, it's just pain. It's a different day. And I can't… I mean, I can imagine a 10, but I don't think I've had a 10. I can imagine a 10 because I'm a haemophiliac and I've had really, really bad bleeds. So, I struggle with the 1 to 10 thing. I generally just toss it at around 6 and leave it alone. It's one of those questions that I don't know how to answer. (Will, 52)

Clinicians recognise the inadequacies of historical care provision around pain in particular. Whilst confident in prescribing medication, they feel they have inadequate knowledge and skills to effectively manage chronic pain in its entirety.

> I think I feel confident in asking the questions. I think how you deal with it is a real… can be a real challenge because, yes, okay, there are certain painkillers that I know how to prescribe, but I'm not a pain expert. (Ruth, Haematologist)

Even with concerns about their own skills and knowledge, clinicians see the need for approaches to pain management to improve so as to enhance care and be considered a normal and effective part of clinical review and intervention choice. PWH need validation of their life experiences in relation to their pain as they want to be part of a solution that works for them, and when it does it is beneficial and highly regarded.

> I think one of the things I've noticed, particularly over the last couple of years, is you're seeing doctors and physios kind of recognising that haemophilia doesn't just occur in a bubble, the kind of text book methods, but actually you have the real life… you know, social life and things have to be fitted around that. And it's been really nice to actually be given a bit more agency and responsibility to make decisions, and actively recognise that there is a lived context to what is possible. (Nick, 30)

Trust in healthcare professionals

Feeling safe, being listened to and knowing that help in managing worries around living with haemophilia is available is important to PWH. Having the option of being able to call or drop into a centre is seen as a vital component of ongoing routine care as well as pain or bleeding that is not resolving as expected.

> for me, it's always been good to have the centre, where I can come and say, "Look, I'm not managing this. Something is wrong. I need help with it. (Tony, 55)

There is clearly a limited experience of pain management approaches that involve a haemophilia multi-disciplinary team intervention or approach. However, attending any other HCP who lacks knowledge of haemophilia is also regarded as ineffective. Barriers to accepting advice or intervention from non-specialists are ingrained in PWH and they are aware this is due to the rare nature of their disease as well as the uniqueness of their physical complaints associated with it.

> I think I… I think haemophilia being reasonably quite a rare condition, I don't think… Having grown up, I don't have a natural trust of any and all clinicians to know why a joint might be the way it is, even if it's quite a generic… even if the joint is damaged in a very generic way. (Leon, 28)

Strategies for pain management

There is agreement with the HCPs and insight from those PWH that strategies employed for pain management are shaped by the life experience of growing up with haemophilia. Pain has always been associated with acute bleeding which can to some degree be managed by factor concentrate. For the most part everything that follows this initial thought process and decision making is linked to both the successes and failures of how individuals chose to manage these pain events.

> Pain is danger. To me, pain means stop and treat yourself. And stop. (Hugh, 65)

Clinicians articulate that PWH coping and living better with pain in adulthood was linked to successes and acceptance of pain in their family and work life. Others reasoned that living with pain was more of a forced acceptance due to the limited unsuccessful options in current healthcare interventions:

> From my side, it is … I think the patients that feel ground down by … it's often too many things at the same time, which are overwhelming for them. And then all the sorts of things that they've done to manage their pain are no longer working, because they're just too overloaded. (Mary, psychologist)

Using pain medication presents a dichotomy of opinion between PWH and clinicians. In an era of limited haemophilia treatment, opioid-based pain medications were standard. Older men with haemophilia have vivid distressing memories of becoming addicted and such addictions being almost ruinous to their life thereafter. Younger men have been socially conditioned to fear addiction from such medications and have as a rule resisted many attempts to take them as prescribed by clinicians even when they probably could be helpful.

> I was under the impression that having … taking painkillers if you had pain, especially in my ankle, meant I might then put pressure on the ankle before was ready to have pressure on it because it wasn't hurting as much. So, I never did. (Greg, 39)

Co-infection with hepatitis C from contaminated blood products had also raised concerns about long term liver health with pain medications and becomes another considered reason why such medications are to be avoided. The avoidance of medication reflects a learned view that pain medications are risky and do not work for pain associated with haemophilia.

Options tried for pain relief exist on a continuum of good and bad consequence. Just to maintain daily activities and mobility PWH face a constant decision making process as to how far to push and challenge themselves within the realms of their daily pain – *'So, it's almost like it's good, bad, but better. I think there is a lot to be said for keeping going sometimes, and just working through the pain to get to a better place.' (Tony, 55)* Although others view such decisions as inevitably ending in failure:

> … I actually am a bit eager and I have requested for physio/exercise referrals. I hope that the exercise would improve stuff, but what I've found is I jump on board each of these programmes with a bit of eagerness, I start trying to climb, and then I realise my joints aren't allowing it, and then I … and then I give up. (Andy, 40)

Uncertain about exercise but clear on what matters

When discussing exercise as a more specific component in managing pain, it was clear that most were uncertain of the rationale to do such a thing. Even with pain there is an acceptance by some, that exercise may provide some positive influence on their health and well-being; however, concerns over possible negative consequences based on previous experiences remain high. PWH identify function and less pain interference in day to day life as most important, and feeling supported to achieve this is essential.

Barriers, enablers, and the need for more proof

Avoidance of bleeding and by default further pain, is by far the greatest barrier to being more active in daily life, and keeps PWH from taking the risk to do more.

> … at the end of the day, people just want to live a pain-free, bleed-free life, and probably taking … people think that taking the more static … not doing something is less risky than doing something. (Leon, 28)

These concerns are recognised by clinicians as a hurdle for PWH in seeing a reason to do more with pain and for how HCPs can facilitate a way through this mind set. However, it also presents the clinicians with a dilemma in that they feel as yet unable to provide 100% assurance that such an approach is indeed safe.

> I think the unknown, is what level of exercise is safe – and I don't think we know that fully. I think we've got … all of us have got ideas, but I suspect there are clinicians who have got different ideas of what's okay to do compared to others. We've got patients who do their own thing too. (Kate, physiotherapist)

Lack of motivation to change the current physical status quo exists with difficulty in conceptualising the benefit of doing exercise when in pain. Day to day activity that fulfils basic needs and requirements is seen as sufficient, and the idea of further physical challenge and exertion makes no sense. Whilst for others, being reassured by the efficacy of prophylaxis on bleeding enabled them to have confidence in "testing" their physical selves in specific exercise activities. This view is echoed by others who view an increase in pain as being less of an issue because its reassurance around bleed risk and after-effects that would encourage them to see exercise as an option:

> … if I need to have a bit of pain and it doesn't come with bleeding, to improve the condition of my joint, I would be more than happy to take that. I would take the pain knowing it's not going to cause a bleed. (Andy, 40)

Practicalities, logistics, and outcomes

Overall both PWH and HCPs were open and accepting of the premise of exercise as a component in pain management. For those that had previous positive experience with exercising with pain, there was a general acceptance that some more pain was acceptable in a longer term view of overall benefit.

PWH were clear that having someone they trust and who understood haemophilia and could understand their fears and anxieties was a key factor in how they would participate, as previous frustrations at non specialists had made them wary. Confidence in knowing they were being advised and shown the correct way to do exercises for example, helped moderate deep seated anxieties about further damage, risk of injury and being safe whilst exercising.

Anticipated personal outcomes were situated firmly in enhanced life participation and living well for PWH, and being able to function well despite their pain:

> I've got … like the example of walking up the stairs to work, stuff like that, and just being able to … Feeling more confident to be … to kind of go out at night to some sort of bar or club and be standing up all night is a big quality of life improvement to me. (Leon, 28)

An acceptance of pain does not necessarily mean there would be no will to have it eradicated if possible, but there appears to be a realistic acceptance of what matters most in their day to lives.

> I want to be kept going, I don't want to be cured, if that makes any sense. (Hugh, 65)

Discussion

The aim of this paper was to explore the experiences, views, and behaviours of PWH and HCPs about pain management and the

use of exercise as a potential component of a management approach. Our analysis highlights that although PWH appreciate and value the expertise of the haemophilia care team, there is a view that they do not feel their pain is talked about or managed well within a haemophilia clinical environment. The current limited options for pain management for PWH remain fraught with fear of consequence and the need for reassurance as to what may be most suitable or effective for them.

Although PWH feel that issues relating to their pain are not captured in current haemophilia clinical setting, they also do not feel comfortable going elsewhere to other non-haemophilia specialists for pain advice, and so therein lies a conundrum. Haematologists and haemophilia centres are considered the primary port of call for pain management advice by PWH [6,11]. However, recent studies suggesting clinicians tend to underestimate pain in PWH [6,18] may help contextualise the reports of those PWH who feel their pain is poorly managed [13]. Our data suggest that such views could be explained in part by the fact that although HCP's acknowledge the need to be able to manage pain within the haemophilia MDT, there is a perception that they do not have sufficient skills and knowledge to help PWH in their clinical care. This phenomenon has not been well documented to date, however, one qualitative study investigating haematologists experiences of managing PWH highlighted the difficulties faced with balancing being an expert in the disease area with the struggle of having to take on other multiple roles but without the necessary knowledge and skills [35]. It is clear that both clinicians and PWH need to find a way to work better together in managing chronic pain, to see people as more than their presenting condition and to identify care concerns and input that is meaningful to all [19].

The lack of a coherent approach to pain assessment in PWH that encompasses both physiological and psychological aspects has been highlighted [8]. For the most part routine, pain assessment has focussed on measuring intensity (VAS, pain rating scales) which PWH do find acceptable in acute bleeds [36]. Participants here perceive a low value to such rating scales for chronic pain, supporting the premise that it is not helpful in modern chronic pain management [37]. It is also reflective of other studies reporting that measuring intensity alone has limitations in PWH [38] and the use of such approaches misses the deeper lived experience and meaning of pain for an individual [39].

The recently updated haemophilia treatment guidelines from the World Federation of Haemophilia highlight pharmacological management as a first line strategy for both acute and chronic pain [40]. In particular, they recommend opioids as an option for chronic pain, whilst others have stated the need to avoid their use in PWH [19] and not to be commenced as a treatment option for those with chronic pain [37]. The participants in this study reported a dislike of pain medications and avoided taking them if at all possible. Perceived non-effectiveness and the dislike of how they made them feel were different to the reasons given in another qualitative investigating masculinity in haemophilia, where avoidance of pain medications was because taking them was viewed as an outward sign of their disorder [41]. Witkop et al. in their questionnaire study of PWH in the USA, noted only 28% took their pain medications as prescribed [42]. Whilst worries about toxicity and lack of effectiveness are common [43] a finding across multiple studies was that if people felt listened to, given appropriate information and were part of the decision making, then adherence and use of pain medications was better [43–45]. Healthcare professionals need to understand the life experiences of PWH to contextualise why they may not want to use pain medications and counsel them appropriately if they are felt to be of use in discrete situations.

'No Aspirin, No Injections, No Exercise' was a common sign seen above the hospital beds of PWH in the 1950 and 1960s, when treatment for active bleeding episodes was limited [46]. Exercise was synonymous with risk and danger of bleeding, and as a result many people went into adulthood with a view that being too active was risky. The narrative histories of those in this study, described in the companion paper to this [29], reflect these past experiences, which are also now being interwoven with trying to navigate and make sense of their chronic pain. The association between risk of musculoskeletal bleeding and physical activity perpetuates still in an era of improved haemostatic treatment. This historical reference point and the personal beliefs developed thereof for many PWH, sits rather awkwardly against a current biomedical paradigm that promotes physical activity for health benefit. Whereas other arthritises such as OA and RA have demonstrated self-management approaches using cardiovascular and strengthening exercise, education and coping skills to be useful adjuncts in pain management [47–50], it remains unclear if this is a safe and feasible approach for PWH. Unlike people with RA who expressed a fear of exercise making pain worse and causing more damage [51], the primary concern voiced here was the uncertainty and meaning of pain sensations. The fear is that being active with pain may provoke bleeding, as well as anxiety that the pain being experienced may actually be a small bleed that could be made worse with being active. This relationship between pain and bleeding has been explored by others who also noted activity avoidance, perhaps somewhat understandable in this context, was a key strategy in managing those fears [28,52,53]. Acknowledging and understanding the fears a PWH may have around their own pain sensations with exercise is important so as to formulate effective and mutually trustworthy interventions for pain management.

Chronic pain in PWH is more becoming more widely recognised as a moderator of physical activity, and by extension for some, planned exercise. Participants in our study were open to the possibility of trying exercise as a treatment option whilst having pain. However, they highlight that their reason to do so related more to being able to function better rather than cessation of their pain, which they acknowledge is unlikely to be "cured". In a qualitative study of men with haemophilia, Taylor et al. [54] reported that their cohort had a very positive approach to exercise and PA and adopted positive coping strategies towards activity. This is in contrast to our study group who appeared more wary of being more active with exercise even though they could reason the benefits. This may be due in part to the participants in this study being recruited due to identifying as having chronic pain, whilst those in the Taylor study were noted to be positive towards PA and exercise as a group. One notable finding similar to ours however was the need to focus on what activities can be done (rather than what to avoid), with a similar focus on enjoyable non-traditional exercise activities (gardening, DIY, walking) being noted in another study by the same author [28].

An understanding of what is realistic, as well meaningful and potentially beneficial to PWH who have pain is important. Recent calls to action for pain management in PWH have highlighted the need for a multi-professional approach recognising the physical, social, and psychological aspects of care [19,55]; however, such an approach has yet to be investigated fully in this population. Current guidelines on pain management in arthritis from the European League Against Rheumatism (EULAR) recommend that a

person centred care approach within a biopsychosocial framework, is delivered by a knowledgeable multi-professional team using a range of interventions that include exercise, social interventions, psychological support, joint specific treatment options, and sleep hygiene [56]. From our data presented here, we demonstrate that such an approach is appropriate, much needed and long overdue in the management of chronic pain in PWH.

We acknowledge that there were limitations to this study. This study was limited to people with severe haemophilia, as historically it is the condition most likely to present with painful multijoint HA. Further investigations should explore if pain and concerns about bleeding influence decision making about pain management options in people with moderate and mild haemophilia. Another limitation may be the number and variety of HCP's who took part in the interviews. Whilst it is possible that increased numbers of profession specific participants would have provided further data, time and resource available for to this study were limited. However as all professionals participating were expert clinicians in haemophilia care, working at five different haemophilia centres, and the fact that haemophilia care is delivered by a multi-disciplinary team, we feel that the views expressed represented a broad view of work practices and experiences.

Analytic process using a RTA approach rather than that of codebook approach to coding was employed here, and so may be considered a limitation in how reproducible the analysis of findings may be. This approach does not seek reproducibility of findings per se, but acknowledges the experience and influence of researcher background on interpretation. A key strength of this study was the condition specific and academic experience of the team. In a rare condition such as haemophilia, the need for this balance is important so as to drive forward quality research approaches that are also relevant to the people taking part in them.

Finally, although barriers and experiences about pain, exercise, and activity have been identified in this paper we do not in any way suggest that they may predict participation in rehabilitation activity. Further research needs to determine if any factors identified here can positively influence participation in a personalised, meaningful pain management programme, of which exercise may be a component.

Conclusions

The need for improved, effective, and meaningful pain management strategies are much needed for PWH who live with long-standing chronic pain. Pain assessment remains perceived as low value, and is coupled with the fact that HCP's in haemophilia feel ill-equipped to engage fully in the process. Even with this dissonance, there is substantial trust and well established therapeutic relationships between those with haemophilia and their healthcare team, providing an excellent foundation on which to build better pain management approaches. PWH want to feel reassured in doing activities that matter to them. It is imperative that pain management approaches are situated within an understanding of the individual's lifetime of pain experiences, framed in the context of modern haemophilia treatments rather than historically inaccurate representations of haemostasis and designed around personally identified goals and functional aspirations.

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Appendix L - Theory of Change Briefing document

BRIEFING REPORT

Background information to inform the development of a Theory of Change model for the REMAP-Haemophilia study.

Background to this project:

Between 35-50% of people with haemophilia (PWH) report living with chronic musculoskeletal pain suggesting that current medical provision is not sufficient for the care of PWH. Those with chronic pain report limitations in mobility and independence, increased anxiety, poor quality of life, and frustration due to restrictions in activities of daily living. Although it is a widespread problem, there are no published guidelines for management of chronic arthritic joint pain in PWH.

The lack of research and guidelines for chronic pain management in PWH means the knowledge, confidence and pathways used by haemophilia clinicians such as haematologists, specialist nurses and physiotherapists, in managing chronic joint pain, is unclear.

It is now well established in other arthritises such as rheumatoid or osteo-arthritis, that rehabilitation based exercise interventions are useful in pain management. But in haemophilic arthritis pain there are very few studies that have established what aspects of rehabilitation, exercise or education may be effective for pain management in PWH.

The overall project aim:

The overall aim of this study is to develop and test the feasibility of a rehabilitation programme using exercise, to improve clinical and self-management of persistent pain associated with haemophilic arthropathy. We want to see if an exercise-based rehabilitation programme can provide a safe and effective intervention for haemophilic arthropathy joint pain, and if it can change an individual's pain symptoms, quality of life and functional ability.

How do we go about trying to design a study to fulfil the aim?

Designing the study involves reviewing and combining data from many sources-

- What other studies have been done before in this area?
  - reviewing the current published literature in haemophilia relating to pain, exercise, physical activity and specific physiotherapy approaches.

- What do published treatment guidelines have to say about pain management?
  - reviewing the World Federation of Haemophilia treatment guidelines

- What can others peoples experiences tell us when thinking about this study?
  - Interviewing people with haemophilia and different healthcare professionals – in-depth exploration of their experiences, views and opinions of pain and its management
  - What do they think about the idea of exercise based rehabilitation for managing pain?
  - What should a study protocol look like? (the theory of change workshop)

- What does the clinical experience of the research study team add to the project?
  - what does my experiences as a specialist physiotherapist bring to this project?

The next sections of this report will describe what information/data we have collated and analysed so far, and how this relates to the workshop meeting on the 4th November 2020.

1. What did a review of the literature tell us?

People with haemophilia report using a variety of methods to self-manage pain that include relaxation techniques, prayer, illicit drugs and rest. Approaches that included prophylaxis with factor concentrate, acupuncture, hydrotherapy, exercise and manual therapy (a physiotherapy treatment approach) have shown some positive effect on both acute and chronic pain. But many of these studies had very small numbers of participants, or, were carried out in other countries with different healthcare provisions (such as access to prophylaxis). So there is some difficulty in being able to conclude with confidence that they would work for most people most of the time.

A review paper looking at studies that used exercise in people with haemophilia found that although exercise was probably safe to do in haemophilia very few studies looked at or measured the effect of exercise on pain .

We then carried out a large detailed review of the literature, looking specifically at the effect of a range of physiotherapy interventions on pain in people with haemophilia. The studies included in this review highlighted a wide range of physiotherapy approaches being used (exercise in water, exercise on land, manual therapy [physio hands on manipulation of joints and muscles], patient education and electrotherapy [machines like laser or using electrical current to help healing or pain]).

The before and after assessment results were analysed using statistical calculations. We found there was a low level of evidence of effectiveness of any one intervention. Analysing how the studies were conducted and written up in the papers highlighted that they were all low quality. For example – many did not describe in enough detail what exercises were carried out – or why those exercises were chosen. For those studies that included patient

education, it is not clear how the need for education was identified or how useful it was to those participating.

There was also no evidence that those participating in the studies were asked their views about it. We do not know if they thought the activities in the study were perceived as helpful or valuable to their lifestyle and their individual needs.

Pain was assessed in these studies using a 0-10 scale only. We do not know if a change in pain intensity meant a change in day to day activity, function or in lifestyle, or if pain was actually something that bothered the people taking part.

A positive however, was that all the studies reported no bleeding or risk to the people taking part. This does add to our view that exercise as a treatment option is worth investigating further.

2. What do the published guidelines say about pain management in haemophilia?

The World Federation of Haemophilia updated their treatment guidelines this year (2020). However, recommendations about pain management relate mostly to the prescription of pain medications. There is still a lack of clarity on the role of physiotherapy and rehabilitation in pain management for people with haemophilia. How to assess pain and its meaning for the person in pain is not addressed in the guideline.

The European principles of care document published in 2008 only mention pain management in the context of a specialist service that PWH could be referred to.

3. What did we learn from analysing the interviews

We interviewed 14 people with haemophilia and six healthcare professionals (two Haematologists, one haemophilia nurse, two haemophilia physiotherapists, one psychologist). The interview data (transcripts of the recorded interviews/focus groups) were analysed and coded (patterns of words, thoughts, meanings, feelings, emotions etc) and then broader themes developed from these codes. The final themes are like the title of a book – in that you have some idea of what the book may be about, but the whole story is more complex. The four overarching themes were:

1. Haemophilia and pain – an evolving life biography

2. Identity and self-agency

3. Haemophilia management and pain management are discordant

4. Uncertain about exercise but clear on what matters

The key findings from this data help us to understand the personal experience of pain as well as how repeated painful events in a lifetime can influence other beliefs and behaviours.

We found that for people with haemophilia, pain has been lifelong and is as much part of their identity as their haemophilia. Pain is almost always initially associated with the thought of a bleed, and it may be that there is more fear of pain being a bleed than just being fearful of pain as a sensation.

There are strong, shared experiences of being advised against (or not allowed to do) activity or exercise when younger in case of bleeding. This has continued into adulthood with a fear of further joint damage with exercise. The fear/anxiety that pain may signify a bleed means that activity is avoided if pain is there –to try and avoid possibly provoking a bleed. But – most agree that this is a difficult sensation to make sense of, with arthritic pain and bleed pain being hard to judge. Especially as many report they find being active can actually help some of the pain/stiffness in their joints.

There is overwhelming trust and appreciation of the care received for management of haemophilia in centres, with specific reference made to the knowledge and expertise of clinicians about haemophilia being key to this. However with regards to pain, PWH and clinicians mention some uncertainty about how well is it managed. PWH verbalise that physiotherapy provisions helps in managing their pain, especially as most do not want to have to take pain medications. PWH would rather be under the care of clinicians who understood them and their haemophilia than having to be referred to an outside medical team.

Exercise as an option to try in managing pain is generally acceptable to both PWH and clinicians. There is a recognition of the need for more knowledge about why pain is there, why rehab based exercise might work and to have assurances that it was safe to do. Having someone 'like me' (i.e. with haemophilic joint disease and pain) describing success with rehab and exercise would be helpful in engaging in this approach. A personalised exercise plan specific to individual physical needs was essential and doing it with a physiotherapist they know and trust was seen as key.

The distances to travel to specialist haemophilia centres was seen as a possible barrier for attending for a rehab group – although no one would want to go locally to a non-specialist either. There were mixed views on doing it either in a class format and doing an exercise session on your own. With the current developing COVID pandemic the consideration for a virtual delivery of the programme became pressing. This was viewed as positive and realistic by PWH for delivering a rehab programme.

4. What will this Theory of Change workshop add?

The aim of this part of the project process is to use the evidence and data collated so far to inform discussions about what needs to be considered in the protocol for the study itself.

The theory of change is a tool that helps to describe the issue to be addressed, the changes we want to make and what we plan to do in the process to make that happen. It is looked at from the real world setting in which the project takes place, including the risks/barriers or opportunities that might influence the change we want to see. The theory of change will provide a detailed framework of the project giving greater confidence in the approach being taken to test our hypothesis.

A key aspect of this method is the co-design approach. That is, working through the process with people (stakeholders) who may both possibly receive the intervention (PWH) as well as those who would deliver such an intervention (physios). They bring real world insight and expertise to the process of developing a plan of action to take forward to test in a study.

There are no right or wrong answers in this process. You as a group will suggest options of what could be included and then discuss how it may or may not incorporate into the framework. There are six main criteria to consider when deciding to include an intervention in the framework.

Is the suggested intervention(s)...

- **Meaningful** – is it described in a way that makes sense to people with haemophilia and the physiotherapists delivering it
- **Well-defined** – is the agreed path of action clear?
- **Do-able** – is it feasible to do it and in the current healthcare and social context?
- **Plausible** – is what we have come up with realistic?
- **Credible** – are people with haemophilia and the physiotherapists doing it likely to believe in it?
- **Testable** – is everything included in the framework specific enough to be able to evaluate and track progress in a credible and useful way

On the day itself...

This kind of workshop is normally done face to face, as the process thrives on social interaction in the group, ideas on post-its, moving ideas and thoughts around, changing your mind etc. However, as you all can appreciate such interaction is now not permitted due to COVID restrictions. Instead we will be trying to recreate the physical workshop experience online!

We will be using a platform called Padlet.com. It will allow ideas/thoughts to be pinned to a virtual board (like post-its) and then as the process develops they can be moved, organised and connected to start to bring together a visual representation of what the study approach should look like (the framework).

We will use Zoom to host the meeting, and my role will be to facilitate the workshop for you. Rather than everyone needing to be logged in to add to the Padlet board themselves, I will log in and share my screen with you. This way we can talk freely on the Zoom platform – and I can type all that is said into the Padlet board. As the session draws to a close we will have developed a visual representation (map) of the proposed study. This map can be considered the key points of the overall process that need to happen in order for the study aims and objectives to be tested.

After the meeting…

I will continue to work on finalising the visual map as well as developing a written narrative report to go along with the map. This will help to provide the levels of detail (discussed in the workshop) that cannot be included in the visual diagram. All of this will be sent to you to review before it is agreed as a fully representative report of the workshop.

Following this I will develop the study protocol that will then be submitted for ethical approval. It is anticipated that we will test the protocol with a small number of people with haemophilia to check it is actually feasible and realistic to run as it is.

Then in about a year or so, we will reconvene to discuss the results of the feasibility study alongside our original ToC map. We will be able to evaluate what worked well and what did not. We will be able to identify from the framework map what links/ assumptions/ interventions may need to change/ edit/ remove in light of the new data from the study.

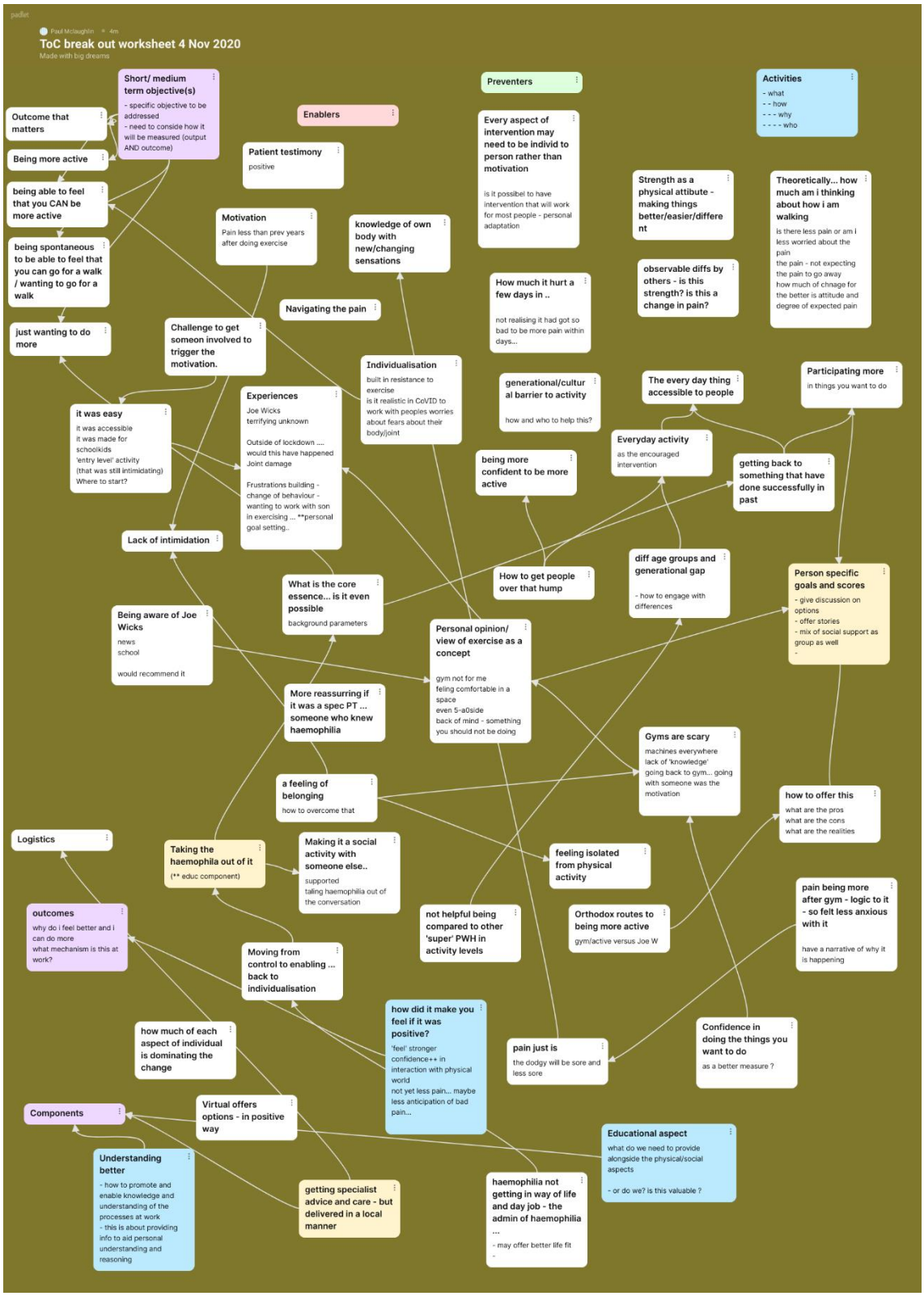
The end result will be a fully informed protocol framework to go forward to test with more people in a bigger trial.

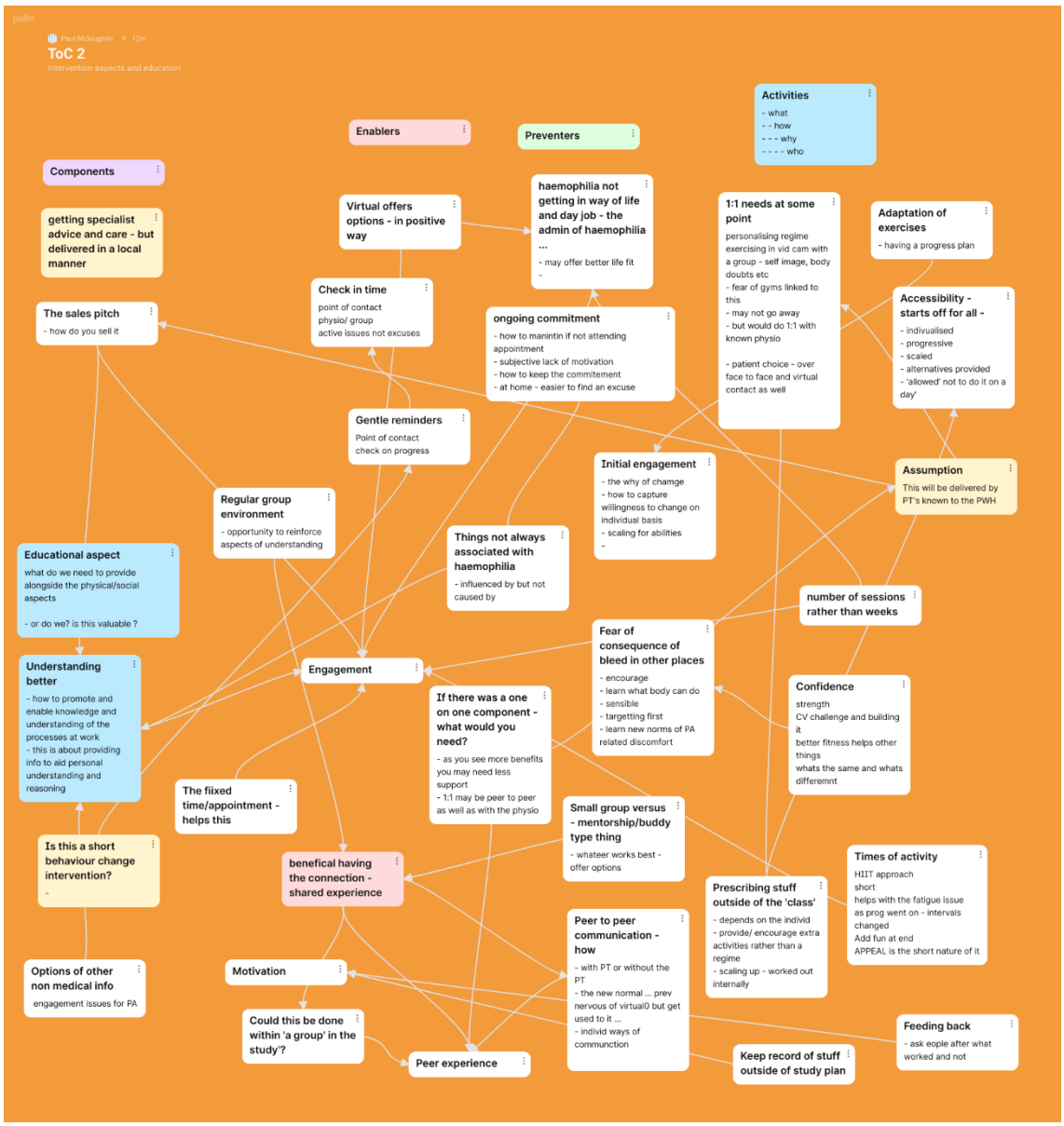
Relevance to haemophilia:

Co-designed studies are rare in haemophilia. We hope to show the value of including PWH in designing studies that they have also helped inform by way of being research participants. It remains unknown if the approach to pain management suggested here will be beneficial in the longer term – but we need to do these studies to find a better way of working with PWH in pain.

Your participation is very much appreciated and I look forward to working with you all on this exciting and novel process.

Appendix M - Padlets from the Theory change workshop




padlet
Paul Mclaughlin · 12m
ToC 2
Intervention aspects and education
Activities
- what
- - how
- - - why
- - - - who
Enablers
Preventers
Components
getting specialist advice and care - but delivered in a local manner
Virtual offers options - in positive way
haemophilia not getting in way of life and day job - the admin of haemophilia ...
- may offer better life fit
-
1:1 needs at some point
personalising regime
exercising in vid cam with a group - self image, body doubts etc
- fear of gyms linked to this
- may not go away
- but would do 1:1 with known physio
- patient choice - over face to face and virtual contact as well
Adaptation of exercises
- having a progress plan
Accessibility - starts off for all -
- indivualised
- progressive
- scaled
- alternatives provided
- 'allowed' not to do it on a day'
Check in time
point of contact
physio/ group
active issues not excuses
The sales pitch
- how do you sell it
ongoing commitment
- how to manintin if not attending appointment
- subjective lack of motivation
- how to keep the commitement
- at home - easier to find an excuse
Gentle reminders
Point of contact
check on progress
Initial engagement
- the why of chamge
- how to capture willingness to change on individual basis
- scaling for abilities
-
Assumption
This will be delivered by PT's known to the PWH
Regular group environment
- opportunity to reinforce aspects of understanding
Things not always associated with haemophilia
- influenced by but not caused by
Educational aspect
what do we need to provide alongside the physical/social aspects
- or do we? is this valuable ?
number of sessions rather than weeks
Fear of consequence of bleed in other places
- encourage
- learn what body can do
- sensible
- targetting first
- learn new norms of PA related discomfort
Understanding better
- how to promote and enable knowledge and understanding of the processes at work
- this is about providing info to aid personal understanding and reasoning
Engagement
Confidence
strength
CV challenge and building it
better fitness helps other things
whats the same and whats differemnt
If there was a one on one component - what would you need?
- as you see more benefits you may need less support
- 1:1 may be peer to peer as well as with the physio
The fiixed time/appointment - helps this
Small group versus - mentorship/buddy type thing
- whateer works best - offer options
Is this a short behaviour change intervention?
-
benefical having the connection - shared experience
Times of activity
HIIT approach
short
helps with the fatigue issue as prog went on - intervals changed
Add fun at end
APPEAL is the short nature of it
Prescribing stuff outside of the 'class'
- depends on the individ
- provide/ encourage extra activities rather than a regime
- scaling up - worked out internally
Peer to peer communication - how
- with PT or without the PT
- the new normal ... prev nervous of virtual0 but get used to it ...
- individ ways of communction
Options of other non medical info
engagement issues for PA
Motivation
Could this be done within 'a group' in the study'?
Peer experience
Feeding back
- ask eople after what worked and not
Keep record of stuff outside of study plan

Appendix N - Health Research Authority confirmation

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Mr Paul McLaughlin

[redacted]

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

Dear Mr McLaughlin

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Physiotherapist-led telerehabilitation intervention for the management of chronic pain in people with severe haemophilia: a non-randomised, mixed methods feasibility study**
IRAS project ID:	**294992**
REC reference:	**21/EM/0161**
Sponsor	**Royal Free London NHS Foundation Trust**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report

(including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **294992**. Please quote this on all correspondence.

Yours sincerely,

Copy to: *Lucy Parker*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
GP/consultant information sheets or letters [GP/Cons letter]	Version 1	18 May 2021
Interview schedules or topic guides for participants [Topic guide end]	Version 1	18 May 2021
Interview schedules or topic guides for participants [Topic guide decliner]	Version 1	18 May 2021
IRAS Application Form [IRAS_Form_11062021]		11 June 2021
Organisation Information Document [REMAP-Haem OID Non commercial]	Version 1	19 May 2021
Other [Response Letter to REC after review]	Version 1	05 July 2021
Participant consent form [Consent TRACKED]	Version 2	05 July 2021
Participant consent form [Consent CLEAN]	Version 2	05 July 2021
Participant information sheet (PIS) [PIS TRACKED]	Version 2	05 July 2021
Participant information sheet (PIS) [PIS CLEAN]	Version 2	05 July 2021
Referee's report or other scientific critique report [NIHR review]		18 May 2021
Research protocol or project proposal [REMAP-Haem Study Protocol]	Version 1	04 June 2021
Sample diary card/patient card [Weekly Diary]	Version 1	18 May 2021
Schedule of Events or SoECAT [SoE]	Version 1	18 May 2021
Summary CV for Chief Investigator (CI) [CV]	Version 1	18 May 2021
Summary CV for supervisor (student research) [Supervisor CV_ M Hurley]	Version 1	24 March 2021
Summary CV for supervisor (student research) [Supervisor CV_ D Stephensen]	Version 1	10 September 2020
Validated questionnaire [BPI]	Version 1	18 May 2021
Validated questionnaire [EQ5D5L]	Version 1	18 May 2021
Validated questionnaire [HAL]	Version 1	18 May 2021
Validated questionnaire [MSK-HQ]	Version 1	18 May 2021
Validated questionnaire [PGIC]	Version 1	18 May 2021
Validated questionnaire [PSFS]	Version 1	18 May 2021
Validated questionnaire [PSEQ]	Version 1	18 May 2021

IRAS project ID	294992

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
Participating NHS organisations will conduct all study activities as per protocol	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	Funding secured from HEE/NIHR ICA Programme Clinical Doctoral Research Fellowship. The Organisation Information Document confirms the funds available to participating NHS organisations from the sponsor.	A PI is expected at participating NHS organisations	It is anticipated that all study activities at site will be conducted by local staff with an existing contractual relationship. No further HR Good Practice arrangements expected

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio.

Appendix O - Research Ethics Committee confirmation

Health Research Authority

East Midlands - Nottingham 2 Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

13 July 2021

Mr Paul McLaughlin
[redacted]

Dear Mr McLaughlin

Study title:	**Physiotherapist-led telerehabilitation intervention for the management of chronic pain in people with severe haemophilia: a non-randomised, mixed methods feasibility study**
REC reference:	**21/EM/0161**
IRAS project ID:	**294992**

Thank you for your letter of 05 July 2021, responding to the Research Ethics Committee's (REC) 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 and Lead reviewer.

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.

Good practice principles and responsibilities

The UK Policy Framework for Health and Social Care Research sets out principles of good practice in the management and conduct of health and social care research. It also outlines the responsibilities of individuals and organisations, including those related to the four elements of research transparency:

1. registering research studies
2. reporting results
3. informing participants
4. sharing study data and tissue

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

	Recommendation
1.	The Committee recommended that an optional statement (yes/no) is added in the ICF which sets out the participant's willingness to participate in the interview part of the study as this is optional on top of everything else.
	Please note that this is only a recommendation and is not a requirement or condition of the REC Favourable Opinion.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

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 management permissions from host organisations

Registration of Clinical Trials

All research should be registered in a publicly accessible database and we expect all researchers, research sponsors and others to meet this fundamental best practice standard.

Health Research Authority

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database within six weeks of recruiting the first research participant. For this purpose, 'clinical trials' are defined as the first four project categories in IRAS project filter question 2. Failure to register a clinical trial is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral:
https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

If you have not already included registration details in your IRAS application form, you should notify the REC of the registration details as soon as possible.

Further guidance on registration is available at:
https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit:
https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the REC with the registration detail, which will be posted alongside other information relating to your project. We are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at:
https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/

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).

After ethical review: Reporting requirements

Health Research Authority

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, including early termination of the study
- Final report
- Reporting results

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC sites

The favourable opinion applies to all NHS/HSC sites taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or management permission (in Scotland) 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/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
GP/consultant information sheets or letters [GP/Cons letter]	Version 1	18 May 2021
Interview schedules or topic guides for participants [Topic guide end]	Version 1	18 May 2021
Interview schedules or topic guides for participants [Topic guide decliner]	Version 1	18 May 2021
IRAS Application Form [IRAS_Form_11062021]		11 June 2021
IRAS Application Form XML file [IRAS_Form_11062021]		11 June 2021
IRAS Checklist XML [Checklist_11062021]		11 June 2021
IRAS Checklist XML [Checklist_15062021]		15 June 2021
IRAS Checklist XML [Checklist_05072021]		05 July 2021
Other [Response Letter to REC after review]	Version 1	05 July 2021
Participant consent form [Consent TRACKED]	Version 2	05 July 2021

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Validated questionnaire [HAL]	Version 1	18 May 2021
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Validated questionnaire [PGIC]	Version 1	18 May 2021
Validated questionnaire [PSFS]	Version 1	18 May 2021
Validated questionnaire [PSEQ]	Version 1	18 May 2021

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.

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 Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at:
https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS project ID: 294992 Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Appendix P - REMAP-Haemophilia study Participant Information Sheet

[LOCAL SITE LOGO HERE]

Participant Information Sheet

STUDY TITLE: Investigating the feasibility of exercise based telerehabilitation in the management of chronic pain in people with haemophilia.

INVITATION

We would like to invite you to take part in our research study.

Joining the study is entirely up to you, before you decide we would like you to understand why the research is being done and what it would involve for you. One of the haemophilia team will go through this information sheet with you, to help you decide whether or not you would like to take part and answer any questions you may have. We'd suggest this should take about 10-15 minutes. Please feel free to talk to others about the study if you wish. We do not expect you to make a decision today, please take your time to think about it after reading this information.

WHY ARE WE DOING THIS STUDY?

Chronic Pain has been identified as an important clinical and personal issue for many people with haemophilia (PWH). Management approaches for chronic pain have focused mostly on advice to take painkillers. However an increasing number of PWH want other ways of managing their pain that does not rely on taking medication. PWH living with pain have told us that they are wary of doing some exercises and activities in case of bleeding. But even with this fear, they would like to feel more confident and supported to be more active and functionally well regardless of their pain.

We want to know if this study can be done the way we have described it.

WHAT DO I NEED TO KNOW ABOUT THE INTERVENTION BEING USED IN THIS STUDY?

In other types of arthritis such as osteoarthritis or rheumatoid, using exercise has been shown to help to improve a person's function and manage their pain. As yet we cannot say if it could be effective for people with haemophilia because it has not been studied in this way before.

This study has been created with the help of people with haemophilia. It uses a low impact, moderate activity exercise approach. It will be delivered virtually using telerehabilitation – that is you will be in your own home on your computer/tablet working with the physiotherapist at the hospital. The exercises will be personalised to you and your own ability. The exercises are mix of strengthening and cardiovascular activities.

WHY AM I BEING ASKED TO TAKE PART?

You are being asked to take part because you have a diagnosis of severe haemophilia A or B, and have told us that you have chronic arthritic pain.

WHAT WILL I NEED TO DO?

The flowchart on page 3 of this information sheet shows the activities and time commitment of the study.

Study questionnaires will assess your pain, physical function and quality of life before starting the six week block of exercise.

Exercises being used are designed to fit a range of abilities and fitness. Your personal exercise plan will be discussed and practised with you before you start the study. Each session will be led by your own physiotherapist and includes a warm up and cool down.

The three knowledge and discussion sessions will focus on pain, pacing activity with pain, and being physically active with pain. These will be led by your physiotherapist and consist of a short presentation followed by group discussion. These will be delivered in a group format and will happen before the group exercise session. Once a week we would like you to complete a short diary about your experiences of the study.

At the end of the six weeks of exercise we would like to do an interview with you. This is because we want to know more information about your experience of taking part in the study, your views on how we conducted the study and the questionnaires we used. This is to help us review the procedure used here and to decide if we need to change or improve on anything. This interview is completely voluntary and will only be done when you have given us consent. We will record the interview and transcribe it (type it up) so that we can analyse the information from it.

12 weeks after you have finished your exercise programme you will be asked to complete the study questionnaires again. We will post these to you at home and include a stamped addressed envelope so that you can send them back to us. This will be the end of your participation in the study.

If you do not wish to take part in the study, we would also like to know why. You will be asked to take part in a 5-10 minute telephone interview with a member of the research team. This is voluntary and we will only contact you with your consent.

Stage 1

- Confirm signed consent for study participation
- Meet with your physiotherapist
- Discuss and agree your goals for taking part
- Practice the exercises and find your own starting level
- Complete the study questionnaires
- Agree dates and times for the exercise sessions in Stage 2
- Practice your computer and webcam set up with the physio
- Time needed: **90 mins max**

Stage 2

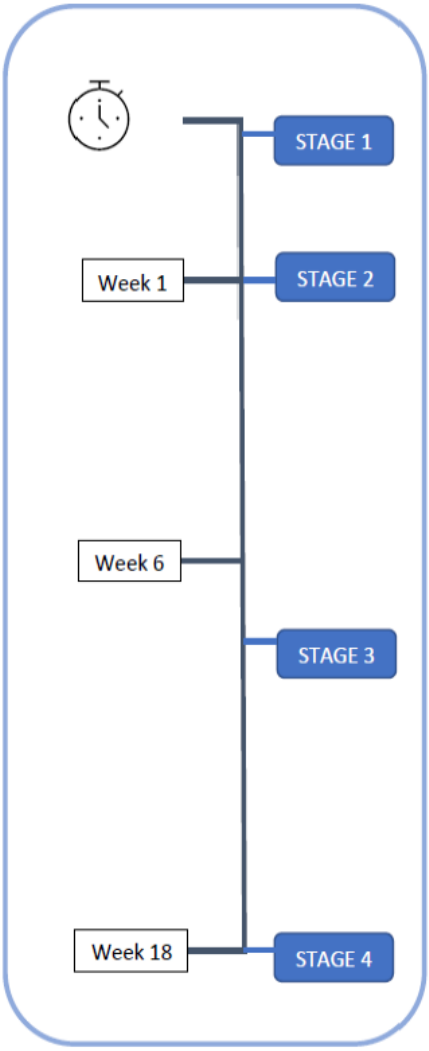
- 12 exercise sessions over 6 weeks plus 3 knowledge and discussion sessions
- Low impact (easy on your joints) and moderate effort (comfortably out of breath)
- Each week: one individual exercise session and one group session
- Each exercise session will be **30-35 mins**
- Week 1, 3, and 5: knowledge and discussion session before the group exercise session (**30-40 mins**)
- Complete the study questionnaires at the end of the six weeks (**40 mins**)

Stage 3

- Consent for end of exercise study interview
- Time and place that suits you (**30 mins**)

Stage 4

- Final follow up assessment 12 weeks after finishing the exercise intervention
- Complete the study questionnaires (**40 mins**).
- No further attendance will be required from you after this



POSSIBLE SIDE EFFECTS

Exercise is generally accepted to be safe for people with haemophilia. We do not expect any significant side effects for you taking part in this study. The exercises included here are low impact (less pressure on joints) and are done at a moderate effort level (being a bit out of breath but still able to talk).

An increase in your pain is a possibility. We are unable to predict if or when this may happen. If this happens you will be able to talk this through with your physiotherapist and alter the exercises if needed.

Some muscle and joint ache can be expected after doing a new activity – but this is normal and will ease after a short while. Bleeding is a low risk due to the type of exercises chosen. Exercise days will be arranged around your prophylaxis days for extra safety.

WHAT IF SOMETHING GOES WRONG

We would not expect you to suffer any harm or injury by participating in this study. If you are harmed by taking part in this study, there is no special compensation arrangement. If you are harmed due to someone's negligence then you may have grounds for legal action, but you may have to pay your legal costs. Regardless of this, if you wish to complain or have any concerns about any aspect of the way you have been approached or treated during the course of the consent process or the study the National Health Service Complaints mechanism is available to you. If you have any concerns regarding the care you have received or as an initial point of contact if you have a complaint, please contact the Patient Advice and Liaison Service (PALS) at the address given below:

PALS office: 020 7830 2174
PALS
Royal Free Hospital,
Pond Street,
London, NW3 2QG

WHAT IF I CHANGE MY MIND

Your participation is entirely voluntary and you are free to withdraw at any time, without giving any reason, without your medical care or legal rights being affected. If you decide to withdraw your consent to participate in this trial, no additional information from your medical records will be collected from that point. Data collected up to the point of withdrawal will be used in the study.

WILL MY INFORMATION BE KEPT CONFIDENTIAL

All information which is collected about you in the course of the study will be kept strictly confidential. All information collected about you that leaves the Haemophilia Centre for the purposes of medical, statistical or regulatory activities related to the study will be identified by your study participant number. No personal identifiable information such as your name and address will be included in these records. If you consent to take part in the research, your data will be handled in a manner in

accordance with the Data Protection Act 2018 and subsequent amendments and the rights you have under this act. The results will be published in various medical journals and international meetings in a way that cannot identify you.

The audio recording of the interview will be deleted after the written transcript has been checked for accuracy. This will be no longer than six months from the time of the interview. Your name will not be included in the transcript, only your study number. No personal data will be included in any reports or write ups.

WHAT WILL HAPPEN TO THE RESULTS OF THIS STUDY?

You will be sent a report of the findings of this study. The information and data gathered as a result will usually be presented at a scientific conference and be written up in a medical journal. No personal identifying information will be included in any of these reports or publications. It is likely we will also share the results of the study through the Haemophilia Society, so it can be shared throughout the UK for patient information and benefit.

These results will also be included in the write up of the final PhD thesis.

Should you wish to see the results of have a copy of any publications, please ask a member of the research team.

WHO IS ORGANISING AND FUNDING THIS STUDY?

The study is sponsored by the Royal Free London NHS Foundation Trust.

This research project is being undertaken as part of a clinical doctoral research fellowship, and forms part of a PhD being undertaken by Paul McLaughlin at St George's University of London. It is funded by the National Institute of Health Research.

Royal Free London NHS Foundation Trust the sponsor for this study is based in the United Kingdom. The sponsor will be using information from you and or your medical records in order to undertake this study and will act as the data controller for this study. This means that Royal Free London NHS Foundation Trust is responsible for looking after your information and using it properly. They will keep any identifiable information about you for 5 years after the study has finished.

You may ask to see the data that has been collected about your health and if you think anything is incorrect, you may ask to have it corrected. However, your rights to access change or move your information are limited, as we need to manage your information in specific ways for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information
https://www.hra.nhs.uk/information-about-patients/

HOW HAVE PATIENTS AND THE PUBLIC BEEN INVOLVED IN THIS STUDY?

To help develop this study we interviewed 14 people with haemophilia who had chronic pain. We asked them about their experiences of pain, how they managed it and what they thought of exercise as an approach. We also asked physiotherapists, nurses, haematologists and psychologists their opinion on using something like exercise to try and manage pain.

Using the findings from these interviews, we then worked together with three people with severe haemophilia and chronic pain to co-design this study. A person with severe haemophilia is also a member of the Research management group and has reviewed all of the information in the protocol and the paperwork associated with it.

WHO HAS REVIEWED THIS STUDY?

This research study has been reviewed by East Midland- Nottingham 2 Research Ethics Committee and the reference number is 21/EM/0161

HOW TO CONTACT US

If you require any further information, please do not hesitate to discuss this with any members of your haemophilia team. You may discuss the study with the principal investigator (your haemophilia physiotherapist), or a member of the haemophilia team/ research team by calling the Haemophilia Centre on 020 7830 2068.

Thank you for taking the time to read this information sheet

Appendix Q - REMAP-Haemophilia study participant consent form

<<(Form to be on headed paper)>>

IRAS ID: 294992

Centre Number: _ _ _ Participant Identification Number for this study: _ _ _

CONSENT FORM

Title of Project: Investigating the feasibility of exercise based telerehabilitation in the management of chronic pain in people with haemophilia (The REMAP Haemophilia study)

Name of Researcher: Initial in box

1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I understand my end of study interview will be digitally recorded and typed up into a transcript for analysis by the research team. I am happy that anonymised quotations may be used in any publications that follow from this interview. ☐
5. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐
6. I consent to the storage of personal information for the purposes of this study. Any information that could identify me will be kept strictly confidential and no information that could identify me will be included in study reports or any other publications. ☐
7. I agree to my GP/Consultant Haematologist being informed of my participation in the study. ☐
8. I agree to take part in the above study. ☐

IRAS ID: 294992

Centre Number: _ _ _ Participant Identification Number for this study: _ _ _

To inform the wider evaluation of this research, we would like to gather information from patients who have been approached to take part in this study but choose not to participate about the reasons for their choice.

Initial in box

9. I do not agree to take part in the above study but I agree to share my reasons for declining in a short interview with a researcher. ☐

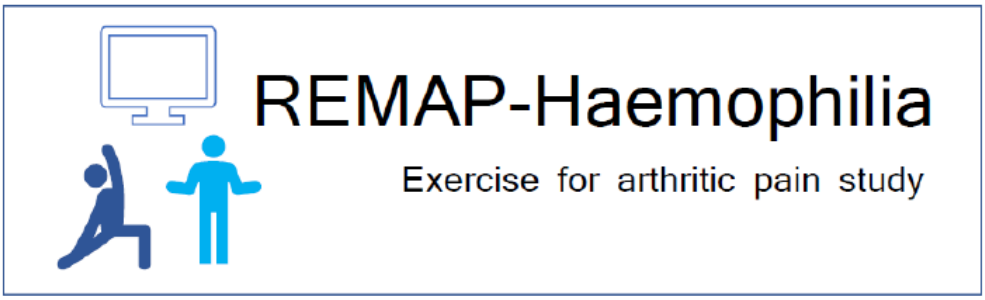
Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix R - Case Report Form (CRF) – REMAP-Haemophilia study

REMAP-Haemophilia CRF Template Version 1 29 July 2021

Date: _ _ /_ _/ _ _ Participant study ID: ☐☐ Study Site ID: ☐☐

Participant Case Report Form



Date: _ _ /_ _/ _ _ Participant study ID: ☐☐ Study Site ID: ☐☐

Study Visit number: _ _

Date: _ _ / _ _ / _ _ _ _

Informed consent

Date of consent: _ _ / _ _ / _ _

Name of investigator taking consent:

_____

Informed consent process discussed with participant ☐

Process of consent to study written in medical notes ☐

Copy of consent given to participant ☐

Copy of consent to medical notes ☐

Copy of consent to study site file ☐

Informed consent version number: Version number: _ _ _ _

Date: _ _ /_ _/ _ _ Participant study ID: ☐☐ Study Site ID: ☐☐

Inclusion Criteria

	Yes	No
People with severe haemophilia A or B		
18 years and over		
Self-reported symptoms of chronic pain associated with haemophilic arthropathy (any joint)		
No history of cardiovascular disease		
No history of pulmonary disease		
Willing and able to give informed consent for participation in this study		
Able to follow instructions		
Have a good command or written and spoken English		
Registered at a UK located haemophilia comprehensive care centre with a named physiotherapist		
Have access to a laptop/ tablet at home and sufficient internet connection		

Exclusion criteria

	Yes	No
Mild or moderate haemophilia A or B		
Any other inherited bleeding disorder		
A diagnosis of chronic pain that is not associated with HA		
Confirmed cardiovascular/pulmonary disease		
Uncontrolled diabetes mellitus		

Demography

Date of Birth	/ /				
Gender:					
Male		Female		Not Say	
Employment:					
Full-time		Part-time		Retired	
Student		Unemployed			
Social History:					
Lives Alone		With partner		With family	
Other		House		Flat	
Sheltered Accommodation					
Main mode of transport:					
Drives		Public Transport		Other	

Ethnicity

Ethnic group	Please Tick
White	
English, Welsh, Scottish, Northern Irish or British	
Irish	
Gypsy or Irish Traveller	
Any other White background	
Mixed or Multiple mixed ethnic groups	
White and Black Caribbean	
White and Black African	
White and Asian	
Any other Mixed or Multiple ethnic background	
Asian or Asian British	
Indian	
Pakistani	
Bangladeshi	
Chinese	
Any other Asian background	
Black, African, Caribbean or Black British	
African	
Caribbean	
Any other Black, African or Caribbean background	
Other ethnic group	
Arab	
Any other ethnic group	

Date: _ _ /_ _ /_ _ Participant study ID: ☐☐ Study Site ID: ☐☐

Medical History – Haemophilia

Diagnosis					
Date of Diagnosis (If known)					
Haemophilia A			Haemophilia B		
Baseline Level (iu/DL)					
Inhibitor status					
Yes		No- never		No- cleared (date)	
Clotting Factor concentrate regime					
Prophylaxis			On Demand		
Type of prophylaxis					
Primary			Secondary		
Tertiary			Unknown		
Clotting Factor:					
Product Name:					
Dose			Frequency		
Bleeding episodes in past 12 months					
Location			Date		
Any known target joints? (As per the ISTH definition – "three or more spontaneous bleeds into a single joint within a consecutive 6-month period")					
Yes			No		
Joint location:					
Joint Location:					
Any problem joints as identified by the participant?					
Yes			No		
Joint Location:					
Joint Location:					
Joint Location:					
Joint Location:					

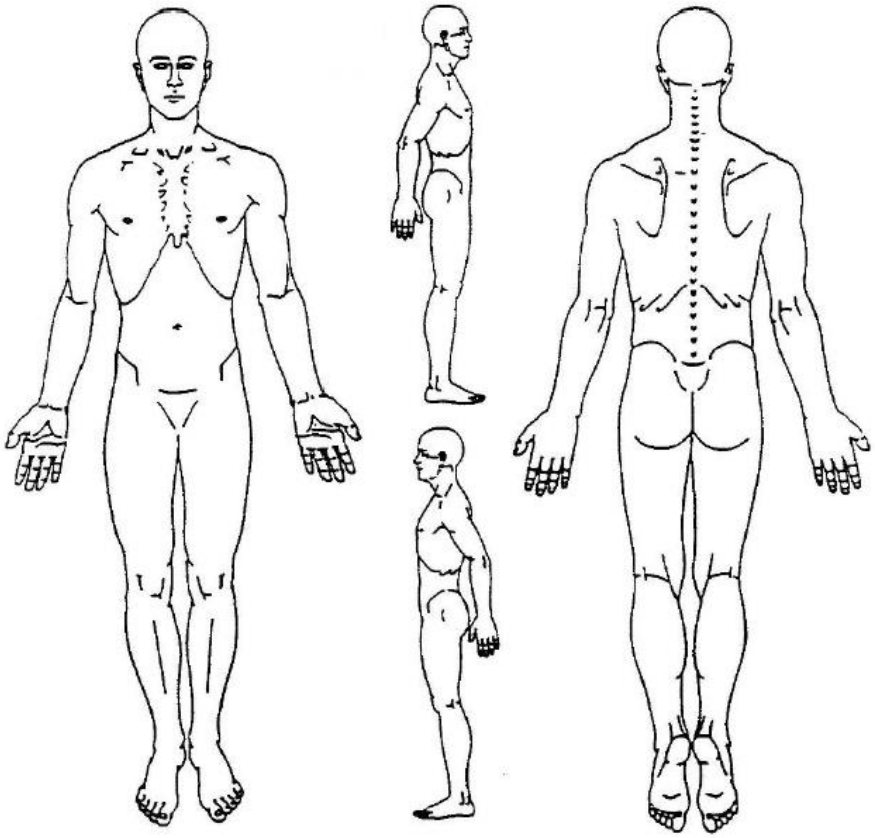
Date: _ _ /_ _/ _ _ Participant study ID: ☐☐ Study Site ID: ☐☐

General Physical examination

Height (cm)		Weight (Kg)	

Please mark on the body chart below:

- Location of joints affected by haemophilic arthropathy (with HJHS score of that joint if known)
- Other MSK issues/deformities of note



Mobility Status			
Independent		Walking stick (x1)	
Elbow Crutch (x1)		Elbow Crutch (x2)	
Zimmer Frame		Wheeled Rollator	
Wheelchair			
Other (please state)			
Splints/supports used (please list)			

Medical History

Co-morbidities and ongoing medical issues	Yes	No
HIV		
HCV		
Heart Disease		
Diabetes		
Liver Disease		
Hypertension		
Pulmonary Disease		
Other (please list):		

Current exercise participation/ physical activity

Activity (as reported by participant)	Frequency

Date: _ _ /_ _/ _ _ Participant study ID: ☐☐ Study Site ID: ☐☐

Surgical History

Body Part (Left or Right)	Procedure	Date

Analgesic Use

Drug Name	Dose	Frequency

Other medications

Drug Name	Dose	Reason for taking

Date: _ _ /_ _/ _ _ Participant study ID: ☐☐ Study Site ID: ☐☐

Self-reported PROMS (study start)

Measure	Checked for completion
Brief Pain Inventory	
Pain Self Efficacy Questionnaire	
EQ 5D 5L	
Musculoskeletal Health Questionnaire	
Haemophilia Activities List	
Patient-Specific Functional Scale	

Signed:

Date:

Appendix S - REMAP-Haemophilia study – Outcome measures

REMAP-Haem BPI | Version 1 | 18 May 2021
IRAS ID: 294992

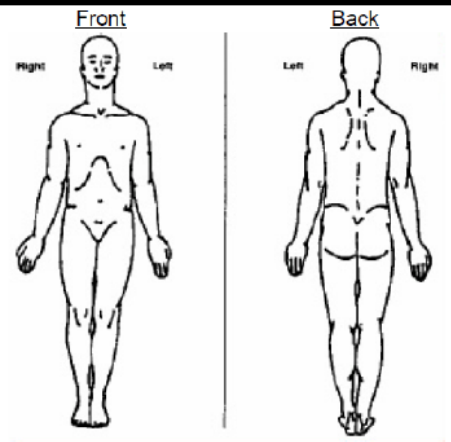
Participant No:	Site Study No:	Date:

Brief Pain Inventory (Short Form)

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ Yes ☐ No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

4. Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

5. Please rate your pain by marking the box beside the number that best describes your pain on the average.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

6. Please rate your pain by marking the box beside the number that tells how much pain you have right now.

☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10
No Pain — Pain As Bad As You Can Imagine

1 of 2

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please mark the box below the percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
☐ No Relief	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐ Complete Relief

9. Mark the box beside the number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

B. Mood

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

C. Walking ability

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

D. Normal Work (includes both work outside the home and housework)

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

E. Relations with other people

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

F. Sleep

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

G. Enjoyment of life

☐ 0 Does Not Interfere ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 Completely Interferes

Health Questionnaire

English version for the UK

Participant number:	
Study site number:	
Date of completion:	

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

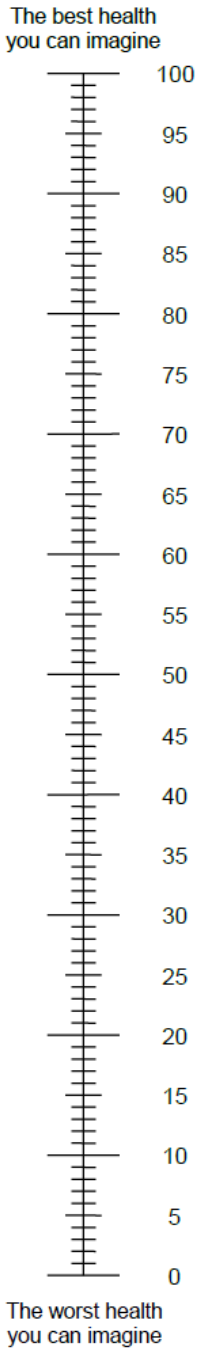
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Haemophilia Activities List

Participant number:	
Study site number:	
Date of completion:	

Introduction

This is the Hemophilia Activities List, or HAL. In this questionnaire several activities are listed that could be difficult for people with hemophilia. The aim of this questionnaire is to see how easy it is for you to do these activities

General comments

When answering the questions, it is only **your own** experience that counts. You should tick the box behind the question that best reflects your own situation.
For every activity, you are asked whether you had any difficulty in performing that activity **due to hemophilia**. There are six different response options. Answer each question by ticking the box that describes your situation.

Example:

In the past month, did you have any difficulty **due to hemophilia** with:

	n/a	Impossible	Always	Mostly	Sometimes	Rarely	Never
Using public transportation (bus, train, subway)	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

For every question you are required to tick one box. The "n/a" response option ("not applicable") can be used if you never (have to) perform that specific activity. The "n/a" option is only available for some activities. The difference between the "Impossible" and "Always" response option, is that with "Always" you are in fact able to perform that activity, but with problems and with "Impossible" you are unable to perform that activity. It is very important that you answer all questions. Even when a question seems irrelevant to you, or when you have no opinion relating to the question, please tick the box that describes your situation most closely.

It will take 5-10 minutes to finish this questionnaire.

Lying down/ sitting / kneeling / standing

In the previous month, did you have any difficulty, due to hemophilia, with:

	Impossible	Always	Mostly	Sometimes	Rarely	Never
Sitting down (e.g. on a chair or couch)	❑1	❑2	❑3	❑4	❑5	❑6
Rising from a chair with armrests	❑1	❑2	❑3	❑4	❑5	❑6
Rising from a chair without armrests	❑1	❑2	❑3	❑4	❑5	❑6
Kneeling / squatting	❑1	❑2	❑3	❑4	❑5	❑6
Bending forward	❑1	❑2	❑3	❑4	❑5	❑6
Kneeling for a longer period of time	❑1	❑2	❑3	❑4	❑5	❑6
Squatting for a longer period of time	❑1	❑2	❑3	❑4	❑5	❑6
Standing for a longer period of time	❑1	❑2	❑3	❑4	❑5	❑6

Functions of the legs

In the previous month, did you have any difficulty, due to hemophilia, with:

	Impossible	Always	Mostly	Sometimes	Rarely	Never
Walking short distances (less than 1 kilometer / 15 minutes)	❑1	❑2	❑3	❑4	❑5	❑6
Walking long distances (more than 1 kilometer / 15 minutes)	❑1	❑2	❑3	❑4	❑5	❑6
Walking on a soft surface (e.g. on the beach or through the woods)	❑1	❑2	❑3	❑4	❑5	❑6
Walking on an uneven surface (e.g. cobblestones, high sidewalks)	❑1	❑2	❑3	❑4	❑5	❑6
Strolling / (window-)shopping	❑1	❑2	❑3	❑4	❑5	❑6
Climbing up the stairs	❑1	❑2	❑3	❑4	❑5	❑6
Climbing down the stairs	❑1	❑2	❑3	❑4	❑5	❑6
Running (e.g. in order to catch the bus)	❑1	❑2	❑3	❑4	❑5	❑6
Jumping	❑1	❑2	❑3	❑4	❑5	❑6

Functions of the arms

In the previous month, did you have any difficulty, due to hemophilia, with:

	Impossible	Always	Mostly	Sometimes	Rarely	Never
Lifting heavy objects	❑1	❑2	❑3	❑4	❑5	❑6
Carrying heavy objects in the arms	❑1	❑2	❑3	❑4	❑5	❑6
Fine hand movements (e.g. closing buttons)	❑1	❑2	❑3	❑4	❑5	❑6
Reaching above your head (to pick something up from a high shelf)	❑1	❑2	❑3	❑4	❑5	❑6

Use of transportation

In the previous month, did you have any difficulty due to hemophilia with:

	n/a	Impossible	Always	Mostly	Sometimes	Rarely	Never
Riding a bicycle	❑8	❑1	❑2	❑3	❑4	❑5	❑6
Getting in and out of a car	❑8	❑1	❑2	❑3	❑4	❑5	❑6
Using public transportation (bus, train, subway)	❑8	❑1	❑2	❑3	❑4	❑5	❑6

Self care

In the previous month, did you have any difficulty, due to hemophilia, with:

	Impossible	Always	Mostly	Sometimes	Rarely	Never
Drying your whole body	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Putting on a shirt, sweater etc.	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Putting on sock and shoes	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Putting on a tie or closing the top button of a shirt	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Going to the toilet	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

Household tasks

In the previous month, did you have any difficulty, due to hemophilia, with:

	n/a	Impossible	Always	Mostly	Sometimes	Rarely	Never
Going out shopping (for food, drink etc.)	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Washing the dishes, cleaning the sink	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Cleaning the house	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Other household tasks (ironing, making the beds)	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Doing odd jobs (both in and around the house)	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Gardening	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

Leisure activities and sports

In the previous month, did you have any difficulty, due to hemophilia, with:

	n/a	Impossible	Always	Mostly	Sometimes	Rarely	Never
Playing games (outdoors, e.g. with your children)	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Sports	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Going out (theatre / museum / movie theatre / bar)	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Hobbies	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Dancing	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Going on a holiday (active)	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
Going on a holiday ("passive"; beach-/hotel holiday)	❑ 8	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

Adaptations and using an aid

To do some activities, you might need some adaptations or an aid. This does not apply to acute bleeding episodes, when you or more or less forced to use crutches to be able to walk. In the following questions we ask you some things regarding those adaptations or aids.

Do you own a car with adaptations?

- ❑ No, I don't have a car
- ❑ No, I don't have adaptations in my car

Yes, I own a car with (multiple responses are allowed):

- ❑ Electronic windows
- ❑ Power steering
- ❑ Automatic gearbox
- ❑ The ability to sit in a wheelchair inside your car
- ❑ Brake and/or accelerator on the steering column
- ❑ Other, namely: .....
- ❑ Other, namely: .....
- ❑ Other, namely: .....

Do you use aids when performing certain activities?

- ❑ No, I don't use any aids

Yes, I use (multiple responses are allowed):

- ❑ A crutch (1 crutch / cane)
- ❑ Crutches (two)
- ❑ Wheelchair
- ❑ Rollator
- ❑ Other, namely: .....
- ❑ Other, namely: .....
- ❑ Other, namely: .....

Thank you for completing the questions on your activities.

Musculoskeletal Health Questionnaire (MSK-HQ)

Participant number:	
Study site number:	
Date of completion:	

MUSCULOSKELETAL HEALTH QUESTIONNAIRE (MSK-HQ)

This questionnaire is about your **joint, back, neck, bone and muscle symptoms** such as aches, pains and/or stiffness.

Please focus on the particular health problem(s) for which you sought treatment from this service.

*For each question **tick** (✓) **one box** to indicate which statement best describes you **over the last 2 weeks**.*

1. Pain/stiffness during the **day** How severe was your usual joint or muscle pain and/or stiffness overall during the **day** in the last 2 weeks?	Not at all ☐ 4	Slightly ☐ 3	Moderately ☐ 2	Fairly severe ☐ 1	Very severe ☐ 0
2. Pain/stiffness during the **night** How severe was your usual joint or muscle pain and/or stiffness overall during the **night** in the last 2 weeks?	Not at all ☐ 4	Slightly ☐ 3	Moderately ☐ 2	Fairly severe ☐ 1	Very severe ☐ 0
3. Walking How much have your symptoms interfered with your ability to walk in the last 2 weeks?	Not at all ☐ 4	Slightly ☐ 3	Moderately ☐ 2	Severely ☐ 1	Unable to walk ☐ 0
4. Washing/Dressing How much have your symptoms interfered with your ability to wash or dress yourself in the last 2 weeks?	Not at all ☐ 4	Slightly ☐ 3	Moderately ☐ 2	Severely ☐ 1	Unable to wash or dress myself ☐ 0
5. Physical activity levels How much has it been a problem for you to do physical activities (e.g. going for a walk or jogging) to the level you want because of your joint or muscle symptoms in the last 2 weeks?	Not at all ☐ 4	Slightly ☐ 3	Moderately ☐ 2	Very much ☐ 1	Unable to do physical activities ☐ 0
6. Work/daily routine How much have your joint or muscle symptoms interfered with your work or daily routine in the last 2 weeks (including work & jobs around the house)?	Not at all ☐ 4	Slightly ☐ 3	Moderately ☐ 2	Severely ☐ 1	Extremely ☐ 0
7. Social activities and hobbies How much have your joint or muscle symptoms interfered with your social activities and hobbies in the last 2 weeks?	Not at all ☐ 4	Slightly ☐ 3	Moderately ☐ 2	Severely ☐ 1	Extremely ☐ 0

Please turn the page and continue

8. Needing help How often have you needed help from others (including family, friends or carers) because of your joint or muscle symptoms in the last 2 weeks?	Not at all ☐ 4	Rarely ☐ 3	Sometimes ☐ 2	Frequently ☐ 1	All the time ☐ 0
9. Sleep How often have you had trouble with either falling asleep or staying asleep because of your joint or muscle symptoms in the last 2 weeks?	Not at all ☐ 4	Rarely ☐ 3	Sometimes ☐ 2	Frequently ☐ 1	Every night ☐ 0
10. Fatigue or low energy How much fatigue or low energy have you felt in the last 2 weeks?	Not at all ☐ 4	Slight ☐ 3	Moderate ☐ 2	Severe ☐ 1	Extreme ☐ 0
11. Emotional well-being How much have you felt anxious or low in your mood because of your joint or muscle symptoms in the last 2 weeks?	Not at all ☐ 4	Slightly ☐ 3	Moderately ☐ 2	Severely ☐ 1	Extremely ☐ 0
12. Understanding of your condition and any current treatment Thinking about your joint or muscle symptoms, how well do you feel you understand your condition and any current treatment (including your diagnosis and medication)?	Completely ☐ 4	Very well ☐ 3	Moderately ☐ 2	Slightly ☐ 1	Not at all ☐ 0
13. Confidence in being able to manage your symptoms How confident have you felt in being able to manage your joint or muscle symptoms by yourself in the last 2 weeks (e.g. medication, changing lifestyle)?	Extremely ☐ 4	Very ☐ 3	Moderately ☐ 2	Slightly ☐ 1	Not at all ☐ 0
14. Overall impact How much have your joint or muscle symptoms bothered you overall in the last 2 weeks?	Not at all ☐ 4	Slightly ☐ 3	Moderately ☐ 2	Very much ☐ 1	Extremely ☐ 0

Physical activity levels
In the past week, on how many days have you done a total of 30 minutes or more of physical activity, which was enough to raise your heart rate? *This may include sport, exercise and brisk walking or cycling for recreation or to get to and from places, but should not include housework or physical activity that is part of your job.*

None	1 day	2 days	3 days	4 days	5 days	6 days	7 days
☐	☐	☐	☐	☐	☐	☐	☐

Thank you for completing this questionnaire.

The MSK-HQ total score is the sum of items 1-14, using the response values provided.

Participant No:	Study Site No:	Date:

Patient Global Impression of Change

Since the start if the study, my overall status is:

1. ☐ Very Much Improved
2. ☐ Much Improved
3. ☐ Minimally Improved
4. ☐ No Change
5. ☐ Minimally Worse
6. ☐ Much Worse
7 ☐ Very Much Worse

REMAP-Haem PSFS Version 1 18 May 2021
IRAS ID: 294992

This useful questionnaire can be used to quantify activity limitation and measure functional outcome for patients with any orthopaedic condition.

Clinician to read and fill in below: Complete at the end of the history and prior to physical examination.

Initial Assessment:

I am going to ask you to identify up to three important activities that you are unable to do or are having difficulty with as a result of your _____ problem. Today, are there any activities that you are unable to do or having difficulty with because of your _____ problem? (Clinician: show scale to patient and have the patient rate each activity).

Follow-up Assessments:

When I assessed you on (state previous assessment date), you told me that you had difficulty with (read all activities from list at a time). Today, do you still have difficulty with: (read and have patient score each item in the list)?

Patient-specific activity scoring scheme (Point to one number):

0 1 2 3 4 5 6 7 8 9 10

Unable to perform activity

Able to perform activity at the same level as before injury or problem

(Date and Score)

Activity	Initial					
1.						
2.						
3.						
4.						
5.						
Additional						
Additional						

Total score = sum of the activity scores/number of activities
Minimum detectable change (90%CI) for average score = 2 points
Minimum detectable change (90%CI) for single activity score = 3 points

PSFS developed by: Stratford, P., Gill, C., Westaway, M., & Binkley, J. (1995). Assessing disability and change on individual patients: a report of a patient specific measure. Physiotherapy Canada 47, 258-263

Participant No:	Site Study No:	Date:

Pain Self-Efficacy Questionnaire

Please rate how **confident** you are that you can do the following things at present, **despite the pain**. To indicate your answer circle **one** of the numbers on the scale under each item, where 0 = not at all confident and 6 = completely confident.

For example:

0	1	2	3	4	5	6
Not at all Confident						**Completely confident**

Remember, this questionnaire is **not** asking whether of not you have been doing these things, but rather **how confident you are that you can do them at present, despite the pain.**

---

1. I can enjoy things, despite the pain.

0	1	2	3	4	5	6
Not at all Confident						**Completely confident**

2. I can do most of the household chores (e.g. tidying-up, washing dishes, etc.), despite the pain.

0	1	2	3	4	5	6
Not at all Confident						**Completely confident**

3. I can socialise with my friends or family members as often as I used to do, despite the pain.

0	1	2	3	4	5	6
Not at all Confident						**Completely confident**

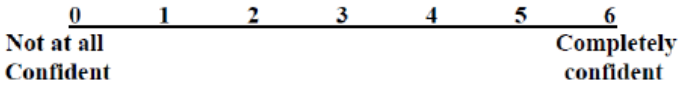
4. I can cope with my pain in most situations.

0	1	2	3	4	5	6
Not at all Confident						**Completely confident**

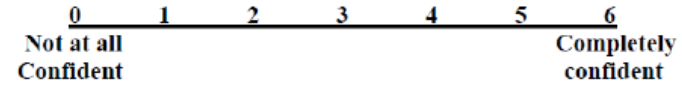
Source: Nicholas M.K. Self-efficacy and chronic pain. Paper was presented at the annual conference of the British Psychological Society. St. Andrews, 1989.

Participant No:	Site Study No:	Date:

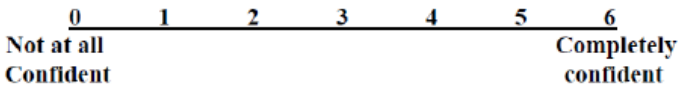
5. **I can do some form of work, despite the pain. ("work" includes housework, paid and unpaid work).**



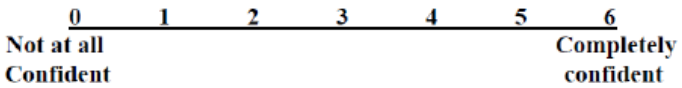
6. **I can still do many of the things I enjoy doing, such as hobbies or leisure activity, despite pain.**



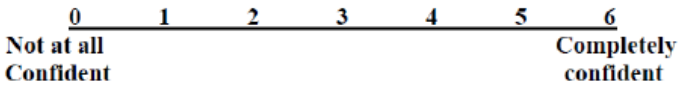
7. **I can cope with my pain without medication.**



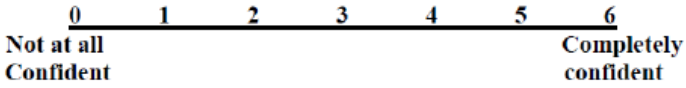
8. **I can still accomplish most of my goals in life, despite the pain.**



9. **I can live a normal lifestyle, despite the pain.**



10. **I can gradually become more active, despite the pain.**



Source: Nicholas M.K. Self-efficacy and chronic pain. Paper was presented at the annual conference of the British Psychological Society. St. Andrews, 1989.

Appendix T - REMAP-Haemophilia Study – PWH participant Diary

REMAP-Haemophilia Study – Participant weekly diary

Research Site: Participant Number:

WEEK 1/2/3/4/5/6
How did you find the exercise sessions this week?
Have you noticed anything different about yourself from taking part in the sessions this week? (pain, mobility, energy etc)

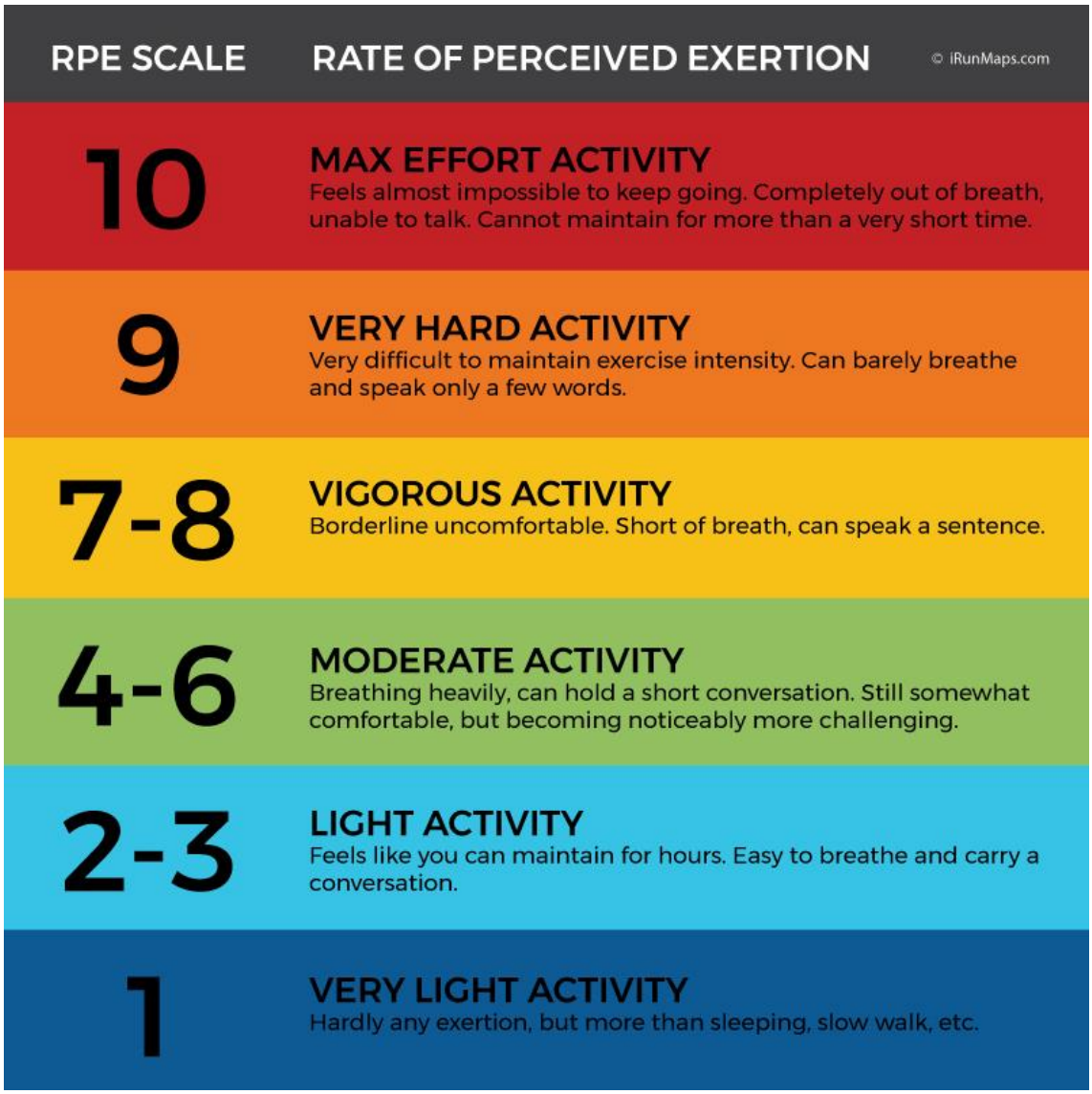
Appendix U - REMAP-Haemophilia Study – Physiotherapist Diary

REMAP-Haemophilia study – Weekly physiotherapist diary

Research Site: _____

WEEK 1/2/3/3/4/5/6	
Physiotherapist issues/ thoughts	
Participant feedback/ issues	
Attendance rates and observed participation	
Individual	Group (both exercise and knowledge sessions)
Technical or other issues	

Appendix V - Rated Perceived Exertion Scale



Appendix W - PowerPoint presentation slides for Knowledge and Discussion sessions

REMAP-Haemophilia

Exercise for arthritic pain study

1

REMAP-Haemophilia

Living with pain and haemophilia

Knowledge and Discussion session 1

2

Session objectives

REMAP-Haemophilia

- Understand better what pain is and why you feel it
- Discuss
  - How pain affects the person in their life
  - How pain exists in haemophilia
- Understand what pain management strategies are being used
- Try to be able to think differently about pain

- Group discussion

3

What is pain?

REMAP-Haemophilia

Definition:

"an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"

Your concept of pain is learned through your life experiences

Your pain experience is influenced by physical, psychological and social factors

Pain may be a signal of injury – but not always

Chronic pain may have negative effect on function and social well-being

Pain is ALWAYS a personal and unique experience

4

Types of pain

REMAP-Haemophilia

- Acute Pain
  - Unpleasant
  - Dynamic physiological and psychological process - days
  - Usually after injury or tissue damage event and related inflammation
  - Role in healing
  - Survival value
- Chronic
  - Unpleasant
  - Persistent physiological, psychological, physical, social process – months/years
  - May or may not have a physical reason for being there
  - No role in healing

Acute and chronic pain can be confusing in haemophilia!

5

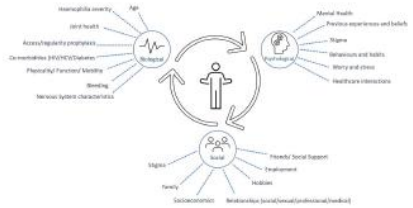
Pain in haemophilia

REMAP-Haemophilia

- Approx 50% PWH report chronic pain
  - So it is very common symptom
- Bleeding
  - Acutely painful, treatable, usually resolves
- Arthritis
  - Chronic pain, up and down, unpredictable
- Difficulty knowing difference between them.
- Concern with what the pain might be – affects behaviour

6

Living with pain



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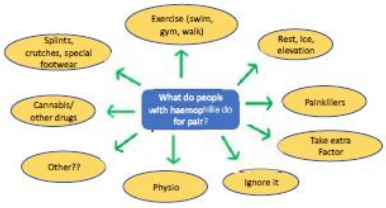
Managing pain



8

Pain as your experience

- Pain is what you say it is!
- For you with your haemophilia
  - May be linked to your experience of treatment
  - Which of your joints are affected
  - How you personally cope with certain things
  - How your daily life exists around your pain
- Is it changeable?
  - Yes – we think so

9

Thinking differently about pain

- What does this pain mean to me now?
- What is the best thing for me to do right now?
- Is this really a bleed?
- Keeping active – maybe sore initially – but getting to a better place
  - Movement is beneficial for arthritic joints
- Ask for help/advice
- Trust yourself and your body
- You are more resilient than you think you are

10

Recap

- Pain is complex
- Your experience of your pain is unique to you
- Pain in haemophilia is both acute and chronic in nature
- Pain being present can affect many aspects of your life
- Understanding your pain better may help you mange it better

11

Discussion session

- All views are valid
- Please share and discuss only what you are comfortable with
- Think about your own experiences and how they may be of use to someone else

12

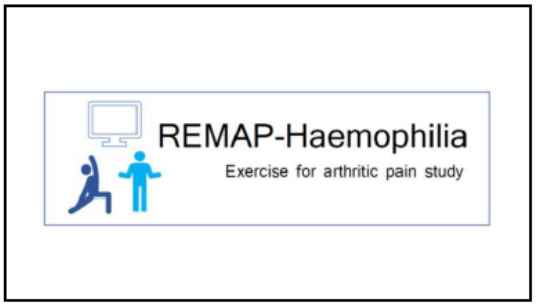
Discussion session

- Does the presentation reflect your experiences?
- How does your pain affect you?
- What do you do that helps your pain?
- Do you have worries about exercise with your pain?

13

Thank you for your time

14



1

Pain and pacing – finding your own level

Knowledge and Discussion session 2

2

Session objectives

- Understand the concept of pacing
- Getting started with pacing
- The importance of goal setting
- How to choose activities
- Progressing activity with pacing

3

Pain and pacing - introduction

- Being active and doing things you want to do with pain can be difficult
- Negative experiences with more pain after movement
  - Makes you avoid doing it
- But – being able to do the things you want is important
- Regular activity can help moderate the pain you feel
- Pacing can help you feel in control
  - Sleep, pain, energy levels, mood

4

Pacing – the concept

- Structured approach to activity
- You regulate what activity you do and when and for how long
- After setting your baseline
  - Gradually increase what you can do
- Idea is to help avoid flaring up of pain
- It's a gradual, learning process
- Works different for everyone

5

Pacing and you

- Balance is the key!
- Avoid doing too much (over pacing) and too little (under pacing)
- It applies to all your activities – work, social, leisure
- Know your baseline
  - Choose activity(e.g. walking, standing) and time how long you can do it comfortably
- ½ this time = your baseline = starting time for activities

6

Goal setting

- Important to identify what YOU want to be better at, do more of etc
- Goals should be personal and meaningful to you
- Think, small achievable steps
- Should be SMART-
- S- be Specific about what you want to do
- M – is it Measurable – can you say when it will be achieved
- A – are they Achievable in the time, and where you are
- R – are they Realistic
- T – are they Timely – is now the right time? How long will you give yourself?

7

Choosing and modifying activity

- Choose what matters to you
- No wrong or right activity
- Work with what your body can do
  - Think about your own affected joints

8

Pacing and progression

- Know your baseline and plan ahead
- When you feel in control then increase time gradually
- Aim to increase 10% on your baseline every week
- IMPORTANT POINT
- Use your baseline on good AND bad days
- Helps avoid 'Boom and Bust'

9

Being kind to yourself

- Plan and prioritise
- Be patient with your approach
- Try and stay consistent in what you do
- Keep at it
- Involve others

- Be kind to yourself !

10

Recap

- Pain can limit what you want to do
- Pacing can be a more structured way to be in control of your activity with pain
- Activities and pacing approaches are individual to you
- Patience is key to making it work best for you

11

Discussion session

- All views are valid
- Please share and discuss only what you are comfortable with
- Think about your own experiences and how they may be helpful to someone else

12

Discussion session

- Does the idea of pacing sound realistic/achievable to you?
- Do you think you would need support to do this?
  - What would this be?
- Thinking about the presentation – do you use any of the concepts already?
- What advice would you give to the group that has worked for you

13

Thank you for your time

14

REMAP-Haemophilia

Exercise for arthritic pain study

1

REMAP-Haemophilia

Physical Activity, pain and haemophilia

Knowledge and Discussion session 3

2

Session objectives

REMAP-Haemophilia

- Understand what is meant by being physically active
- Understand the benefits of being active on health and well-being
- Discuss how haemophilia and pain can impact physical activity
- How much activity is enough
- Choosing activity for you

3

Defining physical activity

REMAP-Haemophilia

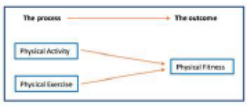
- Physical activity:
  - Any bodily movement produced by skeletal muscles that requires energy expenditure and is a fundamental means of improving people's physical and mental health
- Exercise:
  - Is planned, structured, repetitive, and purposeful so that the improvement or maintenance of one or more components of physical fitness is the objective.

4

Exercise or fitness or activity?

REMAP-Haemophilia

- Physical activity includes exercise **as well as** other activities which involve bodily movement and are done as part of playing, working, active transportation, household chores and recreational activities



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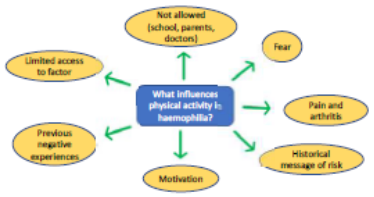
Benefits of being active

REMAP-Haemophilia

6

Physical activity and haemophilia

REMAP-Haemophilia



7

Physical activity and haemophilia

REMAP-Haemophilia

- Now…
- Being active is safe
- Pain may be an issue
  - But OK to be active even with pain
- Pace activities
- Use exercise as part of your physical activity routine
- Use the haemophilia centre for advice if not sure

8

How much and when?

Some is good, more is better

Start today – its never too late

Every minute counts

9

Physical activity is life

10

Choosing your activity

- Meaningful
- Enjoyable
- Fun
- Accessible
- Affordable
- On your own or with others
- Once you start, keep going!

11

Recap

- Being physically active is not the same as doing exercise
- Even with pain and arthritis – being active is important for health
- Little and often is the best way to start
- Choose activities that you enjoy and can do regularly
- Remember – some is good, more is better!

12

Discussion session

- All views are valid
- Please share and discuss only what you are comfortable with
- Think about your own experiences and how they may be of use to someone else

13

Discussion session

1. What does being active mean to you?
2. How does having pain influence your activity levels?
3. What do YOU DO that helps you to be more active?
4. What would HELP YOU to be more active?

14

Thank you for your time

15

Appendix X - REMAP-Haemophilia Study – Post intervention topic guide (PWH)

REMAP Haemophilia feasibility study –
Study completion Participant interview TOPIC GUIDE

Introductions/ Build rapport

- Interviewer/ Interviewee introductions
- Thanks for agreeing to participate
- Overview of purpose of this interview in the wider scheme of the study they have just been part of
- No right or wrong answers – only interested in your views and experiences of taking part

Overall personal experiences and outcome of taking part

- How was your life with your pain before starting this study?
- How has life changed whilst being in this study?
    - How? Why?
- What impact has there been on your pain from being in this study?
- Why did you choose to take part in this study?
    - What did you hope to achieve?
- How did you feel about taking part?
- Did you feel supported by your family/ healthcare team etc?
- How did you find the exercise sessions for you?
    - Were they personalised enough?
- How confident do you feel to carry on with this kind of exercise activity?
- Is there anything you will take from this study into your future?

Questions on feasibility/ study procedures

The next few questions are about how the process of being part of the study was for you.

- Acceptability:
- How were the days and times of the sessions in the week for you?
- (was their enough flexibility, did it fit in with your day)
- How did you find doing the sessions at home on the computer/webcam?
- Did you feel supported by the physio delivering the exercises sessions?
-
- Content:
- What is your opinion on the type of exercises included in the sessions?
- How did you find the length of the exercise sessions?
- (PROMPT: too many, not enough)
- Did you find the content of the knowledge and discussion sessions relevant to you?
- (Can you tell me more about why they were/were not)
-
- The outcome measures used:

What is your opinion on the study questionnaires that we used?
(Prompt: format, length, usability, meaningful)

- Do you think we should have included anything else to measure outcome or change after a study like this?

Any other general feedback

- Has this study changed your perspective on exercise for pain in PWH?
- Were there any unintended benefits from the study for you?
- CLOSE INTERVIEW

-Thank you for your time today-

Prompt/ facilitation phrases:

- Can you tell me more about that?
- How do you feel about that?
- How did that make you feel? (emotional, psychological, physical impact)
- Why do you think that was?
- Could you explain further?

Appendix Y - REMAP-Haemophilia Study – Post-intervention interview topic guide (Physiotherapists)

REMAP Haemophilia Study – Study completion Physiotherapist-

TOPIC GUIDE

Introductions

- Meeting outline
- No right or wrong answers

Overall experience of taking part

- How was taking part in the REMAP study for you?
- Did you feel it was a worthwhile experience?
- Think of the participants in your individual cohorts – did it make a difference to any of them?
- - why?
- - how so?

Feasibility

- Can you tell me how the design of the study was for you?
- - exercise activity session layout
- - times/ days/ length
- How did you find the administration aspects of the study set up?
- - paperwork/ diaries/ time needed
- Do you think the OMs used were appropriate?
- - did they capture change?
- - were they meaningful?

Final thoughts

- Thinking back to the REMAP study – if you had to do it again-
- - what would you like to see done differently
- In an ideal world what would a perfect session look like to you?

Closing

- Any other final comment
- Thanks and close of the meeting

Appendix Z – Use of NVivo to organise datasets and collate identified codes and initial theme development