CHILDREN'S HIPS: INNOVATION IN THE DIAGNOSIS, MONITORING AND TREATMENT OF CHILDREN'S HIP DISEASES

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CONTENTS

LIST OF ABBREVIATIONS

ADHD, Attention Deficit Hyperactivity Disorder

ANOVA, Analysis of Variance

BSCOS, British Society for Children's Orthopaedic Surgery

COMET, Core Outcome Measures in Effectiveness Trials

COS, Core Outcomes Set

COSMIN, Consensus-based Standards for the Selection of Health Measurement Instruments

DDH, Developmental Hip Dysplasia

EEPROM, Electrically Erasable Programmable Read-Only Memory

GP, General Practitioner

GRADE, Grading of Recommendations Assessment, Development and Evaluation

HHS, Harris Hip Score

HOOS, Hip Disability and Osteoarthritis Outcome Score

IMU, Inertial Measurement Unit

IPAQ, International Physical Activity Questionnaires

IPSG, International Perthes' Disease Study Group

LDR, Light Dependent Resistor

LED, Light Emitting Diode

LPA, Light Physical Activity

MANOVA, Multivariate Analysis of Variance

MRI, Magnetic Resonance Imaging

MVPA, Moderate-to-Vigorous Physical Activity

NIHR, National Institute for Health Research

OMERACT, Outcome Measures in Rheumatology

PA, Physical Activity

PE, Physical Education

PedsQL, Pediatric Quality of Life Inventory

PICO, Population Intervention Comparison Outcomes

POF, Plastic Optical Fibre

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROMIS, Patient Reported Outcomes Measurement Information System

PROs, Patient Reported Outcomes

RTC, Randomised Control Trials

ROM, Range of Motion

SCFE, Slipped Capital Femoral Epiphysis

ST, Sedentary Time

TA, Total Activity

VPA, Vigorous Physical Activity

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

LIST OF FIGURES

Chapter 3

Chapter 4

Chapter 5

Chapter 6

Chapter 7

LIST OF TABLES

Chapter 3

Chapter 4

Chapter 5

ABSTRACT

Perthes' disease is an idiopathic osteonecrosis of a developmental hip that is most frequent in Northern Europe. Currently, the absence of a common set of standardized outcomes makes comparisons between studies of different interventions challenging. The overarching aim of this thesis was to understand and enhance the important clinically relevant outcomes that should be measured in Perthes' disease.

A protocol was devised to define a set of core outcomes (COS) (Study 1), which involved a systematic review of the literature, patient and associated family interviews and a Delphi survey. In Study 2, 18 parents were interviewed and perspectives of 12 children affected by Perthes' disease (mean 7.1 years, SD±4.1 years) were explored using a survey tool. Thematic analysis of the parents interviews (main themes n=4) identified a marked effect of the disease on many facets of the child's life, particularly pain and the impact on sleep, play and school attendance. Study 3 followed the guidelines of the COMET-Initiative (Core Outcome Measures in Effectiveness Trials) to define a COS for Perthes' disease. The outcomes from the systematic review, together with the domains collected in Study 2, formed the basis of a Delphi survey (2 rounds), where 18 patients with Perthes' disease, 46 parents and 36 orthopaedic surgeons rated each outcome for importance. A final consensus meeting among representatives of surgeons, patients and parents voted 14 outcomes to be included in the final Core Outcomes Set. Following the systematic review of previous studies (n=112), 33 outcomes were identified. After round 1 of the Delphi survey, participants suggested additional 5 outcomes, therefore a total of 38 outcomes were scored in round 2 of the Delphi. Among these, 16 outcomes (divided in 6 main categories: adverse events; life impact; resource use; pathophysiological manifestations; death; technical considerations) were scored over the 70% threshold for importance. After feedback

from final consensus meeting, a total of 14 outcomes were included in the final Core Outcomes Set (COS).

The results of Study 3 highlighted that hip mobility is an important outcome to measure in clinical trials for Perthes' disease, but to date there is no system able to continuously monitor hip angle in children. Thus, Study 4 aim was to develop a wearable device capable of continuously monitoring joint mobility in both laboratory and everyday life environments. The wearable device developed consists of a microcontroller (ATMEL ATtiny85), with an optical flexible sensor, furnished with a Bluetooth shield (to allow wireless monitoring) and a local storage system (I2C EEPROM), which is worn on the joint of interest. The device demonstrated good accuracy compared to a gold standard goniometer when measuring hip and knee during flexion and extension with a Standard Error of Measurement (SEM) of ±0.27 degrees at 95% confidence interval. When everyday activities were simulated in the laboratory, including walking and sitting (half-squat test), the device was able to retrieve information about the joint angle in real time.

The reduced mobility of the hip joint in childhood hip diseases may affect the physical activity (PA) level of children, promoting a sedentary lifestyle. Study 5 aimed to investigate the relationship between hip mobility (assessed with the current clinical tool for hip mobility- PROMIS questionnaire) and objectively measured PA in children with hip diseases. Twenty-eight children (12 boys and 16 girls) aged between 8 to 17 years old (mean 12±3 years) were recruited for the study. A bivariate Pearson Correlation test (two-tailed) found a moderate correlation between the normal score of hip mobility and the average daily LPA (***r****=0.46,* ***n****=28,* ***p****=0.01*). Additionally, a

moderate to strong positive correlation (***r****=0.67,* ***n****=28,* ***p****=0.01*) between normal scores of hip mobility and increased participation in moderate-to-vigorous PA (MVPA), and a positive moderate correlation (***r****=0.54,* ***n****=28,* ***p****=0.01*) among normal scores of hip mobility and increased participation in vigorous PA (VPA) were found. Children with hip diseases surprisingly reported a higher level of MVPA compared to the general population, however their sedentary time was higher than the general population.

In summary, the work undertaken in this thesis has (i) defined a COS that can be employed in future clinical trials for Perthes' disease; (ii) defined a prototype of a low cost wireless monitor to assess hip mobility, as relevant outcome in the COS for Perthes' disease, in children with hip diseases; (iii) shown that the current clinical tool to assess hip mobility in childhood hip diseases is strongly correlated with objectively measured physical activity. Further research is required to identify and refine the tools to measure the outcomes defined in our core outcomes set.

Declaration

I declare that the work in this thesis is entirely my own and that no portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Publications and presented abstracts arising from this thesis

Journals Papers

Leo, D.G., Lee, W.Y., Gambling, T., Long, A., Murphy, R., Jones, H., Perry, D.C. (2018). The outcomes of Perthes' disease of the hip: a study protocol for the development of a core outcome set. *Trials*, 19: 374-381. (**Chapter 3**)

Leo, D.G., Murphy, R., Gambling, T., Long, A., Jones, H., Perry, D.C. (2019). Perspectives on the Social, Physical, and Emotional Impact of Living with Perthes' Disease in Children and Their Family: A Mixed Methods Study. *Global Pediatric Health*, 6:1-10. (**Chapter 4**)

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Conference Papers

Leo, D.G., Abdullah, B.M., Perry, D.C. and Jones, H. (2019). A Novel Joint Angle Measurement System to Monitor Hip Movement in Children with Hip Diseases. In *International Conference on Applied Human Factors and Ergonomics* (pp. 14-19). Springer, Cham.

Conference Abstracts

Leo, D.G., Murphy, R., Long, W.Y., Gambling, T., Long, A.F., Jones, H., Perry DC. The Outcomes of Perthes (TOP) Study – Development of a Core Outcomes Set for Clinical Trials in Perthes' Disease. Presented at *British Society of Children Orthopaedic Surgeons (BSCOS) Annual Meeting*, Norwich, UK, March 2019.

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A huge hug and a huge kiss to my daughter Miriam, primary source of motivation during my pathway, and to whom this Thesis is dedicated. Daddy loves you.

Finally, many thanks to all my friends, especially to my best friend Paolo and to Alessio and Arianna, for their support during these years.

Dedication

This thesis is dedicated to my daughter, Miriam, that has taught me how to smile, even during the darkest moments.

CHAPTER 1

GENERAL INTRODUCTION

Childhood hip conditions arise after birth or during the first years of childhood and are different in nature and aetiology (e.g. congenic; developmental) (Perry and Bruce, 2011). Among these conditions, Perthes' disease, an idiopathic condition of a developmental hip which induces osteonecrosis of the hip joint, is relatively poorly understood (Wiig, 2009; Perry and Hall, 2011). The disease is more common in boys than in girls, has a higher incidence in North Europe, and the main symptoms are limping, pain and reduced mobility of the hip joint (Westhoff, Lederer and Krauspe, 2019). The main aim in the treatment of Perthes' disease is to preserve the femoral head shape from deformation and to reduce the symptoms of the disease (Westhoff, Lederer and Krauspe, 2019). The treatments for this condition can be either surgical (e.g. pelvic osteotomy) or conservative (e.g. bracing; physiotherapy), but there are not yet common guidelines for the management of the disease and the best treatment option is still under debate in the paediatric orthopaedic community (Hefti and Clarke, 2007).

Core outcomes sets (COS) are defined as the minimum outcomes set to be reported in clinical trials for a specific condition, with the aim to standardise the reporting of results in research studies and clinical trials in order to enable successful and meaningful study comparisons (Clarke and Williamson, 2016). The COMET-Initiative (Core Outcome Measures in Effectiveness Trials) aims to gather researchers interested in the development of COSs, and gives clear guidelines for development (Prinsen et al., 2014). COSs have been successfully applied to different conditions in both children and adults such as colorectal cancer or haemodialysis (Tong et al., 2015; McNair et al., 2016). There are a small number of COSs for orthopaedic conditions (e.g. osteoarthritis) (Rolfson et al., 2016). Given the lack of common guidelines and

debate about optimal treatment in Perthes' disease, the development of a COS would be a constructive approach to allow comparison of studies that investigate the effectiveness of different treatments for this condition, in order to obtain clear guidelines on the best way to manage it. A central theme of the current thesis is to identify, using the COMET-Initiative guidelines, a suite of key physical, emotional and social outcomes to be employed in clinical practice and research into Perthes' disease.

The physical symptoms of Perthes' disease include limping, pain and reduced mobility of the hip joint, which significantly affects the quality of life of children (Marchese et al., 2006; Malheiros et al., 2015; Ramstad, Jahnsen and Terjesen, 2017). Specifically, reduced hip mobility may play a role in the restriction on physical activity participation forcing children with hip diseases to a more sedentary lifestyle and thus the development of related co-morbidities (Keane et al., 2017). Assessing hip mobility and the way in which it influences the physical activity level and the quality of life of children with hip diseases is relevant in the treatment of the disease, and is useful in improving the clinical management of these children. However, current instrumentation and approaches to assess hip mobility (e.g. manual assessment; gait analysis) are confined to measurements in clinics and laboratories (Wang et al., 2019), as current devices cannot assess hip mobility in the daily environment of these children. The spread of wearable technology in healthcare (Bonato, 2010), due to its low cost and easy to wear components, may be pivotal in the development of new methods to assess hip mobility in children. Aspects of this thesis will attempt to develop and characterised a wearable sensor to measure hip mobility during everyday life as well as assess the relationship between current clinical tools to assess hip

mobility and objectively measured everyday physical activity in children with hip diseases.

CHAPTER 2

LITERATURE REVIEW

2.1. HIP DISEASES IN CHILDREN

Hip diseases affect children with varying clinical significance and severity. The causes of paediatric hip disorders include congenital (developmental dysplasia of the hip), developmental (Perthes' disease); infectious (septic arthritis); inflammatory (juvenile rheumatoid arthritis); traumatic (slipped capital femoral epiphysis - SCFE); and neoplastic (osteochondroma) conditions (Perry and Bruce, 2011; Zucker et al., 2013). The main issue in the diagnosis of these conditions is the non-specificity of the symptoms (Perry and Bruce, 2011; Zucker et al., 2013). The child usually reports hip pain, hip irritability or begins limping, which are often confused for growing pain related-symptoms thus making clinical evaluation difficult. To have an accurate diagnosis, it is essential to use imagery (such as x-ray or magnetic resonance imaging – MRI) to establish the specific nature of the symptoms (Carpineta et al., 2007).

Hip diseases impact the mobility of the hip joint, which induces serious limitations in the daily life of the children (Engesæter et al., 2011). Hip stiffness is induced by damage to the hip joint and from the pain that the child experiences when trying to move the leg. Damage to the hip joint at this age can also lead to early osteoarthritis in the adulthood (Carney, Weinstein and Noble, 1991). Although hip mobility is an important parameter to take into consideration during clinical evaluation of hip diseases and to measure the effectiveness of the treatments, there are limited tools in clinical practice to assess severity or changes following any intervention. The current methods are either subjective self-assessment questionnaires (Ramsey et al., 2001; Malheiros et al., 2015) or require expensive laboratory/clinic equipment (e.g. gait analysis; manual and electrical goniometers) (Mohamed, 2012) which are generally complicated to use and time-consuming.

The focus of this literature review is two-fold; firstly to understand the developmental paediatric hip condition, Perthes' disease, and describe the issues in clinical diagnosis and treatment of this disease. Secondly, to summarise the current monitoring systems available to assess hip mobility in clinical environments and as tool for diagnosis and monitoring interventions.

2.2. PERTHES' DISEASE

Legg-Calvé-Perthes disease (also known as Perthes' disease) is an idiopathic avascular necrosis of a developmental femoral head, which induces shape deformation of the hip joint (Perry and Hall, 2011; Perry et al., 2012e). The disease has its onset usually between 4 and 8 years of age, and it is more common in boys than in girls (4:1) (Perry and Hall, 2011; Perry et al., 2012e). Its incidence is higher in North Europe (especially in UK and in Norway), with 1 case per 1200 children per year (Wiig, 2009; Perry et al., 2012e). The radiological view of Perthes' disease is characterised by evidence of sclerosis of the femoral head, which is flattened and fragmentised (Joseph, 2015; Westhoff, Lederer and Krauspe, 2019). It is still unclear what factors start the necrotic process, but it is thought that this process is linked to dysfunction or injury within the blood vessels that supply the femoral head (Nelitz et al., 2009). The causes of the disease are not well defined, with major hypotheses suggesting socio-economic deprivation (e.g. nutritional deficit) and exposure to tobacco smoking during pregnancy as potential causes (Nelitz et al., 2009). The disease usually heals itself over a period of 3-4 years from the onset of the first symptoms, but if left untreated, femoral head deformity is highly probable (Perry and Hall, 2011; Westhoff, Lederer and Krauspe, 2019). The management of Perthes' disease aims to prevent femoral head collapse, which can be obtained with containment methods, which are either of

surgical or conservative nature (Westhoff, Lederer and Krauspe, 2019). However, there is debate on the best management strategy for the disease, with clinical management varying from country to country and even from surgeon to surgeon (Hefti and Clarke, 2007).

The disease has a highest incidence in male children, and it is more common in white children, with 1 to 3 cases per 100,000 children under the age of fourteen (Perry et al., 2012e). Geographical distribution sees its highest incidence in the Northern areas of the UK (such as Liverpool and Scotland) with an average of 10 cases per 100,000 children under the age of 14 years (Perry et al., 2012e). The general incidence of the disease has declined over the last 20 years in areas where index of deprivation has been reduced (e.g. in the Merseyside area the incidence of the disease declined from 17 to 9 cases per 100,000 children under the ages of 14 years between the 1976 and the 1995), suggesting a possible correlation between the socioeconomic conditions of these children and the incidence of the disease (Perry et al., 2012e).

2.2.1. Clinical Relevance of Perthes' Disease

Despite spontaneous recovery of the femoral head's blood supply which halts osteonecrosis, the disease leaves serious consequences for the hip joint (Moghadam, Moradi and Omidi-Kashani, 2013; Palmen et al., 2014a). The fragmented epiphysis behaves like an unossified cartilage, and the shape is easily malleable by the external forces acting on the hip joint (from surrounding muscles and tendons; and from bearing of weight). These shape deformations can lead to flattening of the femoral head or its misshape, which results in hip pain; joint limitations and possible early osteoarthritis in the adulthood (Perry and Hall, 2011). Therefore, early and accurate

diagnosis of the disease with the most appropriate treatment is required to reduce its symptoms and related complications.

2.2.2. Signs and Clinical Presentation

Patients usually report initial symptoms of pain in the hip, groin or knee, which are more severe with movement (Perry and Bruce, 2011; Perry and Hall, 2011). Limping is also common. The range of motion (ROM) of the hip joint is reduced, and a leg length discrepancy can also be present. Moderate or intense activity (such as walking for long distances or running) can increase irritation and inflammation of the damaged area, with intense pain. Clinical examination alone is often inadequate and Perthes' disease is often confused with growing pains by general practitioners who have no previous experience with the disease, thus delaying the correct diagnosis (Perry and Bruce, 2011). The disease usually affects only one leg, but 10% of the cases present bilateral manifestations (Nelitz et al., 2009). A late age of onset; severe limitations of the hip ROM; being overweight; and female sex are all risk factors for a poor outcome (Nelitz et al., 2009).

Diagnostic evaluation of the disease is performed through lateral x-ray, which can show different stages of the disease progression following Waldenstron's classification (Joseph, 2015; Westhoff, Lederer and Krauspe, 2019):

1) **Early Stage:** which is difficult to assess, with the only clear abnormality related to the widened joint space of the affected hip compared to the contralateral side;
2) **Sclerotic Stage:** this stage has more evident alteration of the hip joint, as the femoral head shape begins to alter, with increased density (sclerosis), and loss of epiphysis' height – contributing to flattening;

3) **Fragmentation Stage:** where the breaking of the epiphysis is evident;
4) **Healing Stage (or Late Stage):** the sclerotic bone tissue has been removed and new bone tissue formation is evident. The central part of the epiphysis is usually the last to re-ossify.

2.2.3. Pathophysiology of Perthes' Disease

It is thought that the avascular necrosis of the femoral head which induces the disease is due to the occlusion of the only vessel that supply blood to the epiphysis at the early age of the symptoms onset (the lateral ascending epiphyseal artery – a branch of the medial circumflex artery) (Perry and Hall, 2011). However, explanations as to why this vessel becomes occluded it is not yet clear. The study of Perry et al. (2012c), showed that in children affected by Perthes' disease there is a reduction in small arteries calibre and function, which support the possible vascular nature of the disease and suggest the genetic aetiology of the condition. Children affected by the disease show a whole body growth abnormality, and are usually reported as smaller than their peers (Perry and Hall, 2011). A tendency of hyperactivity has also been reported as behavioural characteristics of affected children (Hailer, Haag and Nilsson, 2014b), but there is not yet enough evidence to support it and more research is required.

The cause of Perthes' disease is not completely understood. However different hypothesis have been suggested, which are related to (Bahmanyar et al., 2008; Perry and Hall, 2011):

1) **mechanical failure:** where the hyperactive behaviour of the child can lead to activity level beyond its bone age and thus damages the epiphysis initiating the avascular necrosis process;

2) **vascular compromise:** such as intraluminal obstruction (e.g. coagulopathies) or extraluminal compression (such as accumulation of fluid within the hip capsule), which can start the avascular process;
3) **nutritional deficiency** (especially focused on the absence of manganese): which may act prenatally and suggested as direct observation of the socioeconomic background of the majority of children affected by Perthes' disease;
4) **exposure to tobacco smoking:** which can induce damage of the vascular endothelium that starts during the pregnancy from smoking mothers.

A part from the above, which are the most supported in literature, additional causes have been suggested as main factor in the development of Perthes' disease. However, the studies are often controversial. For example correlation between low birth weight and the development of Perthes' disease has been supported by different studies (Lappin et al., 2003; Sharma, Sibinski and Sherlock, 2005; Metcalfe et al., 2016), with other studies excluding it as primary factor involved in the aetiology of the condition (Wiig et al., 2006; Daniel et al., 2012; Perry et al., 2017). Additionally, different studies have suggested that a genetic factor may play a role in the development of Perthes' disease (Miyamoto et al., 2007; Su et al., 2008; Kannu et al., 2011), with focus on a mutation of the collagene type II gene (COL2A1) proposed as the trigger factor of the condition. However, investigation into the main factors that induce Perthes' disease is still required.

2.2.4. Treatments for Perthes' Disease

The clinical treatment of Perthes' disease aims to reduce pressure on the hip joint and to contain the femoral head inside the acetabular cavity in order to prevent further deformation of the necrotic bone tissue and reduce pain (Joseph, 2015). Several options have been proposed to obtain containment, which can be either surgical (femoral and pelvic osteotomy) or conservative (bracing; non-weight-bearing approaches) (Nelitz et al., 2009; Joseph, 2015; Westhoff, Lederer and Krauspe, 2019):

1) **Pelvic osteotomy:** Pelvic (or shelf) osteotomy is a surgical extension of the acetabular roof, which aims to cover the uncovered anterolateral femoral epiphysis to increase the protection of the femoral head. The use of Pelvic osteotomy has increased in the recent years, due to its promising results (Bulut et al., 2014) in improving femoral head protection and due to the possibility to allow children to be mobilised on crutches within days after the operation;
2) **Femoral Osteotomy:** Femoral (or varus) osteotomy is the most common form of surgical treatment for Perthes' disease, which aims to redirect the head of the femur inside the acetabulum. Children are then kept immobilised for around 6 weeks after the surgery with the use of a plaster (full leg);
3) **Bracing:** The Petrie Cast (a bilateral cylinder plaster cast) is a conservative approach aimed to contain the femoral head in the acetabulum via leg abduction. The cast is required to be worn for 2 to 3 years. A number of concerns have been raised about this treatment method due to the prevention of mobility and lower limb physical activity of the children for this long period of time;
4) **Non-weight-bearing approach:** The use of a wheelchair and/or limitations in weight bearing activities for children affected by Perthes' disease have been

widely suggested as treatment option for many years and it is still advised in some hospitals or countries. The aim is to reduce the weight bearing impact on the hip joint in order to preserve shape deformation of the femoral head until the natural healing process is completed. This method of non-weight-bearing is used alone as a conservative approach to the disease, or as support to surgical treatments.

5) **Physiotherapy:** is suggested by some surgeons to support conservative (bracing and non-bearing method) and surgical approaches.

Despite the options above, the best treatment for Perthes' disease is still unclear with no agreement in the paediatric orthopaedic community (Hefti and Clarke, 2007). Indeed, the clinical management of these children varies from country to country and even from hospital to hospital of the same country (Hefti and Clarke, 2007). This lack of consensus is related not only to diverging opinions among surgeons, but also to the differences in symptoms presented by the patients, with some of them showing mild symptoms that do not require surgery and can be managed by conservative approaches, and others showing more severe symptoms that is deemed as needing urgent surgery. In addition, different surgeons use different indicators to decide if the patient needs treatment, with some basing their decision on radiological classification, and others basing it on the patient's age or on the degree of the hip range of motion. However, the most important limitation to clear guidelines for the management of Perthes' disease is the lack of standard outcomes to report the success of any intervention (Chapter 3 and 5). The need for standard outcomes sets to be reported in clinical trials has already been discussed in the literature (Williamson et al., 2012; Clarke and Williamson, 2016), highlighting its importance in the definition of clear guidelines for different diseases. The COMET-Initiative (Prinsen et al., 2014) aims to define

standard core outcomes sets for different pathologies. COSs are the minimum set of outcomes to report in clinical trials to define success of treatment, in order to have published studies that report similar outcomes and are then easy to compare, contributing in performing meaningful meta-analyses. Due to a lack of a current COS for Perthes' disease, studies on this disease have usually reported different outcomes, making it impossible to compare results through meta-analysis or other approaches, and making difficult to state which is the more appropriate treatment for the condition. There is no doubt that having a standard outcomes set to assess efficacy of treatments in clinical trials for Perthes' disease would be the first step to clarify the best way to treat it. The development of a COS for Perthes' disease is a central aim of the current thesis.

2.2.5. Prognosis

More than 80% of the cases of Perthes' disease have good or very good outcomes up until the age of 40. Following this approximately 50% of the cases require artificial hip replacement around the age of fifty (Hailer, Haag and Nilsson, 2014b; Joseph, 2015; Westhoff, Lederer and Krauspe, 2019). Prognosis depends on a number of factors, such as sex; age at the time of the onset of the symptoms (with children diagnosed before the age of 6 having the best prognosis); limitations of the hip ROM; and radiographic evidence of "femoral head at risk signs" (e.g. subluxation of the femoral head; lateral epiphyseal calcification) (Nelitz et al., 2009). Different prognosis classifications of the disease have been suggested and the most common, presented in chronological order, are (Catterall, 1981; Nelitz et al., 2009; Kollitz and Gee, 2013):

1) **Catterall classification (1971)**: which is based on the extent of the involvement of the femoral head. This has limited reliability and prognostic value;
2) **Salter and Thompson classification (1984):** defined by the extent of subchondral fracture present in the x-ray in the early stage of the disease. This classification is only relevant for cases diagnosed at their early stage;
3) **Herring classification (1992):** based on the height of the lateral pillar of the epiphysis of the femoral head. This classification has the greatest prognostic value when determined in the early fragmentation phase of the disease.

2.2.6. Physical Activity in Children with Perthes' Disease

It is well known that Physical Activity (PA) is important at every age, and especially during childhood, having beneficial effects on health (e.g. reducing obesity; increasing bone density); psychological development (e.g. reducing anxiety); and improve quality of life (e.g. improving cardiovascular health) (Fedewa and Ahn, 2011; Pradinuk, Chanoine and Goldman, 2011; Reiner et al., 2013; Chaplais et al., 2018). Children affected by Perthes' disease, and hip conditions, should not be exempted from doing physical activity, which performed with precaution is an optimal tool to improve some related symptoms of the disease (e.g. hip mobility; reducing pain) and also in helping children to do not feel excluded from their peers (e.g. during playing or physical education) (Strong et al., 2005).

PA in Perthes' disease has been poorly investigated in literature, with only a single study assessing subjectively reported physical activity in patients (adults and children) with Perthes' disease in Sweden (Hailer, Haag and Nilsson, 2014b). Curiously,

children affected by Perthes' disease reported a higher PA level compared to their peers (assessed with the use of health related and physical activity questionnaires). This has been suggested as a tendency of these children to be hyperactive (Hailer, Haag and Nilsson, 2014c; Hailer and Nilsson, 2014), although additional research is needed to support it. Despite this study, literature on the topic is still poor and hypothesized that children with hip diseases have a lower level of physical activity and demonstrate a more sedentary lifestyle, similarly to children affected by other chronic diseases (Maggio et al., 2010). Surgeons often show divergent opinion on the PA level that children with Perthes' disease should perform. Indeed, some of them completely discourage it (recommending the use of wheelchairs for clinical management), while some of them advise to keep the usual level of physical activity that the child previously had (only avoiding high impact activity such as jumping on trampolines). Additionally, impaired hip mobility in children has been correlated to a poor quality of life (Marchese et al., 2006; Ramstad, Jahnsen and Terjesen, 2017) and may play a role in the reduction of their PA level. The exclusion from physical activity participation induces these children to a sedentary behaviour, which can cause consequential co-morbidity (e.g. metabolic diseases; cardiovascular diseases; and obesity) (Goran, Ball and Cruz, 2003; Keane et al., 2017) which would also worsening the disease symptoms (e.g. overweight can increase the pain on the hip joint). No study to date has objectively investigated the PA level of this population and if it is influenced by the hip mobility and this will be the focus of chapter 7 of the current thesis.

2.3. Summary

The management of Perthes' disease aims to reduce the shape deformation of the femoral head, involving treatments that aim to confine the femoral head inside the acetabulum to protect it. The treatment methods used can be either conservative or surgical, but no clarity on the best method has been reached yet, leaving the treatment decision based more on the personal preferences of the orthopaedic surgeon in charge than on scientific evidence. The uncertainty of the best treatment for Perthes' disease is also supported by the lack of a standard outcomes set for this condition that does not allow results of the studies to be compared. This thesis aims to define, following the COMET-Initiative guidelines, a COS for future clinical trials in Perthes' disease and assess the relationship between hip mobility and physical activity.

PART II - 2.4. ASSESSING HIP MOBILITY IN CHILDREN WITH HIP DISEASES

2.4.1 Hip Mobility in Children Hip Diseases

Joint mobility is an essential requirement of an individual to perform the daily living activities without limitations and avoid possible injuries (Sankar, Laird and Baldwin, 2012; Reiman and Matheson, 2013). In children with hip diseases, including Perthes' disease, hip mobility is often reduced due both to mechanical limitations (e.g. weakness of the surrounding muscles; osteoarthritis of the joint) and to pain (Perry and Bruce, 2011; Zucker et al., 2013). This reduction in joint mobility affects the daily life of these children reducing their ability to perform routine tasks (such as walking down the stairs or taking part in sport including physical education lessons in school)

and play with peers or siblings (Engesæter et al., 2011; Malheiros et al., 2015). Hip mobility is thus an important parameter to define the degree of limitations that hip conditions induce to the child as well as an important parameter to keep in mind while evaluating the outcomes of treatments for the disease. Despite this, methods to assess hip mobility currently used in clinical practice are limited. Some, although easy to implement in clinical practice are unreliable in the measurement (e.g. manual assessment), others are more reliable but expensive and/or difficult to implement in clinical practice (e.g. gait analysis systems). Importantly, no device is able to measure hip mobility in the daily environment of children affected by hip diseases, which would provide key information as to what activities these children are limited to perform as a consequence of the hip disease.

2.4.2. Current Methods to Assess Hip Mobility

Hip mobility assessment is performed (in both children and adults) with different approaches that varies based on the availability of instrumentation and on the experience of the health care professionals performing the assessment. The most common method used in clinical practice to assess hip mobility is the use of healthy questionnaires (e.g. Harris Hip Score - HHS; Hip disability and Osteoarthritis Outcome Score - HOOS) (Nilsdotter and Bremander, 2011). Such questionnaires investigate the degree of limitations induced by hip diseases in relation to common tasks (e.g. walking down the stairs with or without using a railing) or symptoms (e.g. reporting of pain). Despite the ease of use, low cost and speed of completion employing this approach, this measurement tool is subjective and has limited reliability.

Another common method used to assess hip mobility in clinical practice is the manual assessment of the joint performed by the health care professional or the surgeon (sometimes with the help of a manual goniometer) (Owen, Stephens and Wright, 2007; Sankar, Laird and Baldwin, 2012). This method involves a passive manipulation of the leg through the physiological range of motion of the hip joint to check for stiffness in the movement and for reduced mobility of the joint. Again, although this is an easy and fast method to assess hip mobility and a cheap solution to be used in clinical practice, this procedure is affected by the experience of the person performing the assessment and the perception of stiffness, which can vary between health care professionals.

More accurate methods to assess hip mobility exist and are usually present in specialised clinics/hospitals and in research laboratories. These methods use gait analysis (through a series of cameras and sensors) and electronic goniometers (which measure joint motion during movements) to assess hip mobility, with high accuracy and reliability in its measurements (Mohamed, 2012; Carse et al., 2013; Wang et al., 2019). Due to the high accuracy of these methods to assess hip mobility, they are currently the gold standard for the evaluation of this parameter. Nevertheless, these methods have some limitations. Firstly, these methods are expensive (with gait analysis systems that can reach costs up to £250, 000; and electronic goniometers costs up to £1,000; with additional maintenance costs) (Wang et al., 2011; Carse et al., 2013). Additionally, these systems need to be used by qualified technicians due to their complicated functions and specialist equipment. This makes these methods difficult to use in everyday clinical practice. Secondly, because these methods can only be used in laboratory/clinical setting and cannot monitor conditions during everyday life, they can only make a general assessment of the patient's hip mobility,

which is assessed outside of the living environment of the patient and influenced by the joint stiffness felt only on the test day. Indeed, hip stiffness can change during bad and good days, which is a variable that cannot be controlled during laboratory tests, inducing the possibility to obtain only partial and often misleading data from this procedure. Thus, there is the clear need to develop a more effective methods to monitor this parameter not only in an accurate and reliable way, but also allowing monitoring of the joint through the day and in the daily environment of the patient, while keeping the general costs low.

2.4.3. Wearable Technology to Monitor Hip Mobility

Wearable technology is an emerging trend in healthcare, and systems that aim to remotely measure health parameters (such as heart rate or blood glucose levels) are already on the market and largely used in clinical practice (Bonato, 2005; Bonato, 2010). The advantages of such technology is the low cost implementation and the small size of the devices which allow easy implementation in the patient life to monitor health status for prolonged periods of time. The features of these devices, which can include connection to Bluetooth or WiFi interfaces (Paradiso et al., 2008), allow easy transmission of the collected data and remote monitoring of the patient's health status that does not disrupt daily tasks in the daily environment.

A device to measure hip mobility with such characteristics including small, low cost, transmittable data that is wearable during everyday life would be ideal in clinical practice for childhood hip diseases. Thus, the following paragraphs aim to describe the generic components of wearable technology systems and summarise the

advantages of this technology in the development of a wearable system able to monitoring hip mobility in children affected by hip diseases.

2.4.3a Overview on Wearable Technology for Healthcare Measurements

Wearable sensors are electronic sensors that are worn on the human body with the aim to collect physiological and movement data of a patient to monitor health status (Bonato, 2003; Bonato, 2010). There are different types of wearable sensors depending on the data they aim to collect (Bonato, 2005; Bonato, 2010). For example, sensors may monitor vital signs (e.g. heart rate); track body movements (e.g. walking); or monitor environmental conditions (e.g. light exposure). Physiological parameters of interest are usually heart rate; blood pressure; blood oxygen; respiratory rate; and muscle activity. Additionally, biochemical sensors allow the monitoring of parameters such as blood glucose, even allowing continuous drug administration based on blood glucose level for example. The use of wearable technology in rehabilitation has focused on the development of sensors for body movement detection and tracking (Hecht et al., 2009). In this field, applications of accelerometers, gyroscopes, mechanical pressure and flexion sensors are most common.

These sensors are part of custom-designed devices that are able to wirelessly communicate to other electronic devices (such as smartphones or smartwatches) to allow patients to get real time feedback (Kramer et al., 2011); or to communicate via the internet (e.g. WiFi) to transfer the collected data to online databases for interpretation by clinical practitioners and/or researchers (Paradiso et al., 2008; Hoang and Chen, 2010). Advantages of these devices are related to (i) remote monitoring of the patient's status for prolonged periods of time; (ii) the possibility for the health care

professionals and researchers to collect and monitor the patient's status in their daily life activities; and (iii) the ability for the patients to obtain real time feedback from the device itself. However, despite these advantages, some limitations are still present in wearable technology applied to healthcare (Lewy, 2015), such as limitations due to the battery duration (which influences the extension of the monitoring process of the device); to the data transmission security which needs enhanced protocols of data encryption to avoid lack of sensitive information outside the designed channels; and the distrust of the patients (especially the oldest ones) to embrace this kind of technology.

2.4.3b Components of a Wearable Device for Health Monitoring

Wearable technology for health monitoring applications usually uses multiple sensors to form a sensors' network that can integrate data from either body-worn sensors only or body-worn sensors in addition to environmental sensors (Kang et al., 2010; Reinkensmeyer et al., 2012). Advances in microelectronics and microcontrollers have allowed miniaturisation of devices which where cumbersome into small monitors that can easily fit inside clothes or watches (Bonato, 2005). These devices operate at low energy, reducing the battery consumption and prolonging the device monitoring time, and have low-cost components that reduce the overall price of the final product to allow widespread distribution.

A wearable device for health monitoring is usually composed by three main building blocks:

1) **main Microcontroller:** which is the processor unit that gathers data from the sensors network and analyses the data;

2) **Sensors' Network:** that collects data of interest from the body or the environment;

3) **Wi-Fi or Bluetooth module:** that allows wireless transmission of the data to devices (e.g. smartphones) or to the internet (e.g. online databases).

2.4.3c Wearable Technology in Children Hip diseases

As reported above, the current methodology to assess hip mobility in children affected by hip conditions lacks a reliable and cost effective tool that can be implemented into patients' daily routine. Low-cost and ease of use are key features of a tool capable to assess hip mobility in children, additionally with the features of comfort and the ability to remotely collect joint motion data. Indeed, it is essential that this tool can be used in the child's daily routine. This feature is fundamental to assess hip mobility in daily activities and in the natural environment of the children, to define the degree of limitations that these conditions have on the child's life and thus improve their management. The widespread of wearable technology in healthcare, which has been demonstrated to be positively accepted by patients in the monitoring of their health parameters, and the high reduction in costs of the main components required to build up these devices, are key components in the development of a specific device to assess hip joint mobility in children. Fundamental characteristics of this new device would be the easy implementation in clinical practice, with the reliability of the measurements and containment of the costs, and to be easy to worn for remote monitoring by patients. Study 4 aims to develop and characterise a new low cost, wearable device to measure hip mobility in daily life.

2.5. Summary

Hip mobility has been shown to be a key factor to assess the limitations that children affected by hip conditions face daily and to assess the effectiveness of treatments. To date no current ambulatory or laboratory system can monitor hip mobility in the daily environment of the child. Such a device will be of interest for orthopaedic surgeons; physiotherapists; and clinical researchers to monitor the impact that hip mobility has on the daily activities of affected children. This would allow the assessment of limitations in the daily environment of the child to seek for better understanding of the daily limitations induced by hip diseases, as well as to improve monitoring in joint mobility after or during treatments.

AIMS AND OBJECTIVES OF THE THESIS

The overarching aim of this thesis is to understand and enhance the important relevant clinical outcomes that should be measured in Perthes' disease.

The study specific aims of the thesis are:

1. In study 1 to outline a protocol to define a COS for Perthes' disease.
2. In study 2 to determine the social, physical and emotional impact of living with Perthes' disease on affected children and their family (caregivers).
3. In study 3 to identify, using the COMET-Initiative guidelines, a suite of key physical, emotional and social outcomes to be employed in clinical practice and research into Perthes' disease.
4. In study 4 to characterize a low cost wearable joint angle monitoring system to assess hip mobility in children with hip diseases during everyday life.
5. In study 5 to assess the relationship between PROMIS (Patient-Reported Outcomes Measurement Information System) assessed hip mobility and physical activity level in children with hip diseases.

The aims outlined above will be achieved through the following objectives:

In line with ***Aim 1***:

1. Follow the COMET-guidelines to outline a protocol to develop a core outcomes set for future clinical trials in Perthes' disease.

In line with ***Aim 2***:

1. Design and implement a specific children booklet to seek Patient Reported Outcomes (PROs) from children with Perthes' disease;

2. Collect PROs from the families of children affected by Perthes disease using semi-structured interviews.

In line with ***Aim 3:***

1. Conduct a systematic review of the literature relating to clinical trials in Perthes' disease to obtain a list of outcomes used in previous studies;
2. Summarise PROs of patients affected by Perthes' disease and their parents using the data obtained from study 2;
3. Conduct a Delphi survey summarising the outcomes obtained from the above points to seek opinion from surgeons, patients and parents from around the world;
4. Conduct a final consensus meeting to define the outcomes of importance to be included in a COS for future clinical trials for Perthes' disease.

In line with ***Aim 4***:

1. Program a low cost micro-controller to gather data from a flexible optical sensor;
2. Implement a local data storage to save data during daily monitoring;
3. Build a working prototype of the wearable sensor that can be worn by the participant;
4. Collect joint angle data during movements of everyday life.

In line with ***Aim 5***:

1. Use accelerometers to collect data on the physical activity of children with hip diseases;
2. Use the PROMIS Paediatric Item Bank v2.0 – Mobility Short Form 8a (lower limbs) as an index hip mobility in children with hip diseases;

3. Correlate PROMIS score with accelerometer measured physical activity.

CHAPTER 3

THE OUTCOMES OF PERTHES' DISEASE OF THE HIP: A STUDY PROTOCOL FOR THE DEVELOPMENT OF A CORE OUTCOME SET.

The contents of this chapter were published in: **Leo, D.G.**, Leong, W.Y., Gambling, T., Long, A., Murphy, R., Jones, H. and Perry, D.C., **2018**. The outcomes of Perthes' disease of the hip: a study protocol for the development of a core outcome set. *Trials*, 19(1), p.374.

3.1. INTRODUCTION

Perthes' disease is an idiopathic osteonecrosis of the hip in childhood. It most commonly affects boys between 4 and 8 years old (Perry, Skellorn and Bruce, 2016). The highest incidence of Perthes' disease is in Northern Europe, particularly the Northern part of the UK (Perry et al., 2012b) and Norway (Wiig, 2009). Perthes' disease generates a susceptibility of the femoral head to change shape, due to the forces acting across the joint (Perry and Bruce, 2011; Perry and Hall, 2011). These shape changes alter the way that the joint moves, which can cause lifelong pain, functional limitations and accelerate the development of osteoarthritis (Stulberg, Cooperman and Wallensten, 1981).

Clinical treatments focus on the prevention of femoral head collapse, restoring the range of motion and improving the functional recovery (absence of pain, amount of usual daily activity and sport related activity) of the children (Karimi and McGarry, 2012). Even though there are many published studies investigating effectiveness of various surgical or non-surgical treatments, there is no consensus for the best management approach in the paediatric orthopaedic community (Karimi and McGarry, 2012). In fact, there are no standard outcome methods to assess the success of treatment, which results in difficulties when trying to make comparisons between studies.

The absence of standard outcomes is one of the important pieces of feasibility information required before definitive intervention studies can begin. The development of Core Outcome Sets, popularised through the COMET-Initiative, is the approach that has been developed to formulate a set of standardised outcomes particularly for use in clinical research such as randomised control trials (RCT)

(COMET-Initiative, 2018). COSs in clinical trials seek to reduce heterogeneity of the outcomes, reduce bias, improve the accuracy of data interpretation and allow meaningful comparisons between studies facilitating meta-analysis (COMET-Initiative, 2018).

Currently, a small number of COS have been developed within orthopaedic surgery, such as for hip fractures (Haywood et al., 2014) or on generic total joint replacement (Singh, Dohm and Choong, 2017). To date no COSs are available to determine the success of interventions used in the treatment of Perthes' disease of the hip in childhood.

3.2. AIM AND OBJECTIVES

3.2.1. Aim

The aim of this study was to outline a protocol to develop a COS for Perthes' disease treatment in children, which can be used in clinical and cost effectiveness studies (COMET-Initiative, 2018).

3.2.2. Objectives

1. Systematically review the current literature to identify outcomes used in previous studies of interventions for Perthes' disease;
2. Identify outcomes important to children and parents through an interview process;
3. Prioritise the outcomes from key stakeholders, such as surgeons, physiotherapists, and family doctors (GPs) using a Delphi survey;

4. Conduct a consensus meeting where the outcome list will be discussed with all stakeholders, and parent and child representatives to form the core outcomes list.

3.3. METHODS/DESIGN

3.3.1. Systematic Review

The aims of the systematic review are to identify the primary and secondary outcomes in both operative and non-operative intervention strategies for Perthes' disease. All randomized control trials, cohort studies and case series, that include patients treated for Perthes' disease, irrespective of their treatment type, that report childhood outcomes of the disease, will be included. Following the PICO (Population Intervention Comparison Outcomes) approach, the inclusion criteria are here summarised:

- **Population:** Children with Perthes` disease;
- **Intervention and comparator:** any treatment;
- **Outcomes:** any outcomes.

All studies must involve humans and all studies must be in English language. This review will be limited to manuscripts in English, which have been published since 1990. The systematic review aims to generate a list of all outcomes measures used in the current literature.

3.3.2. Selection of studies

The search strategy will identify all published papers on the management of Perthes' disease. Databases involved in the search will be **the Cochrane Library, PubMed**

and **Web of Science**. Multiple databases will be used to maximize the sensitivity of the search strategy. The time period searched will be between January 1990 and January 2017.

3.3.3. Eligibility of studies

Studies will be selected by 2 reviewers (D.G.L. and W.J.L.) who will screen all the titles and abstracts. Titles of articles will be reviewed and included or excluded using Rayyan software (Ouzzani et al., 2016). Full text of all the manuscripts that match the inclusion criteria or manuscripts in which the abstract does not give enough information to make a clear decision about their inclusion, will be obtained. This process will be documented with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow-diagram (Moher et al., 2009).

3.3.4. Data extraction

Data from eligible studies will be extracted through the data extraction form. This involves identification of the primary objective, prospective/retrospective data collection, study type, population, number of patients, conservative management, surgical management, primary and secondary outcomes measured, outcome assessment tools, follow-up.

3.3.5. Data analysis and presentation

All outcomes reported in eligible studies will be extracted and tabulated with their definition and measurement method(s), and then categorized in domains. To ensure the comprehensiveness of COSs, outcomes terms will be assigned to one of the five core domains of the OMERACT (Outcome Measures in Rheumatology) framework (Boers et al., 2014), that include the areas that should be covered by outcomes measures in order to ensure an adequate reporting of the results. The five domains of

the OMERACT filter 2.0. are divided in: *1) adverse event*; *2) life impact*; *3) resource use*; *4) pathophysiological manifestations*; and *5) death*. As suggested by (Dorman et al., 2018), the additional sixth domain of "technical considerations", not included in the original OMERACT filter, will be included in order to assess technical or surgical outcomes that surgeons use to quantify successful outcomes. Under this domain will also be assessed the feasibility of use in clinical practice of the reported outcomes (Long and Dixon, 1996). All six areas, related to the purpose of the review, are listed in table 3.1.

Table 3.1. Modified OMERACT filter 2.0. core areas.

Core Area	Core Domains	Example(s)
Adverse events	Adverse Events	Unintended consequences
Life impact	Physical/Social/Emotional/ Cognitive/Health Related Quality of Life	Quality of life, pain, impact on family, absence from school, participation in sports activities, functional scores – hip ROM and gait impairments
Resource use	Economic/Hospital/Need for intervention/Social burden	Length of stay, further surgery, physiotherapy
Pathophysiological manifestations	Musculoskeletal	Femoral head collapse, healing process, impingement
Death	N/A	N/A
Technical considerations	Technical/Surgical considerations	Radiographic measurement Feasibility of use in clinical practice

3.4. IDENTIFICATION OF KEY OUTCOMES TO PATIENTS AND PARENTS

3.4.1. Overview

Patients and parents opinions will be investigated and integrated in the COS development process through the identification of Patient-Reported Outcomes through semi-structured interviews administered to the patients and their parents, in order to assess the life impact of the disease (Macefield et al., 2014). Patient involvement is a fundamental step in order to define the COS, following the COMET guidelines (COMET-Initiative, 2018). PROs identified through semi-structured interviews will be added to outcome list obtained from the systematic review. The full list will then be submitted for the experts' evaluation through the round 1 of the Delphi Survey.

3.4.2. Interview Process

In order to determine the PROs for children with Perthes' disease, the process will include two stages (figure 3.1):

1. Parents, will be interviewed through a semi-structured interview process;
2. Children, which with the help of the parents and/or of the interviewers (if needed) will complete a bespoke booklet to report their PROs. This booklet was initially designed with the help of two families affected by Perthes' disease to ensure that it was sufficient to extract all of the relevant information. The booklet is used as a prompt to develop further discussion with the children.

Sample size will ensure insight into a diverse range of parent and child perspectives. The aim is to recruit up to 40 participants, 20 with parents and 20 with their child with

Perthes' disease. The sample size estimation is based on general qualitative research guidelines (Baker and Edwards, 2012), and it will be deemed complete when there will be agreement that saturation is reached, with no new outcome domains generated. The sample will purposively select a range of children aged 5 to 16 years, both boys and girls, at different stage of the disease (pre or post-surgery, or treated with conservative approaches). The aim is to provide a richness in perspectives while remaining feasible within resource constraints. Data representing a variety of perspectives and from a diverse sample helps to enhance the credibility of findings by demonstrating that the researcher has sought to present a balanced picture and not favoured one particular viewpoint or perspective (Rubin and Rubin, 2011). Participants will be selected from patients attending Alder Hey Children's Hospital Liverpool (UK), from members of the Perthes' Association (UK) and via families known to the International Perthes' Disease Study Group (IPSG).

Inclusion into this part of the study for children (and their parents) are related to history of Perthes' disease in the child (irrespective of the current stage of disease, and treatment method), and the ability to be conversant in English.

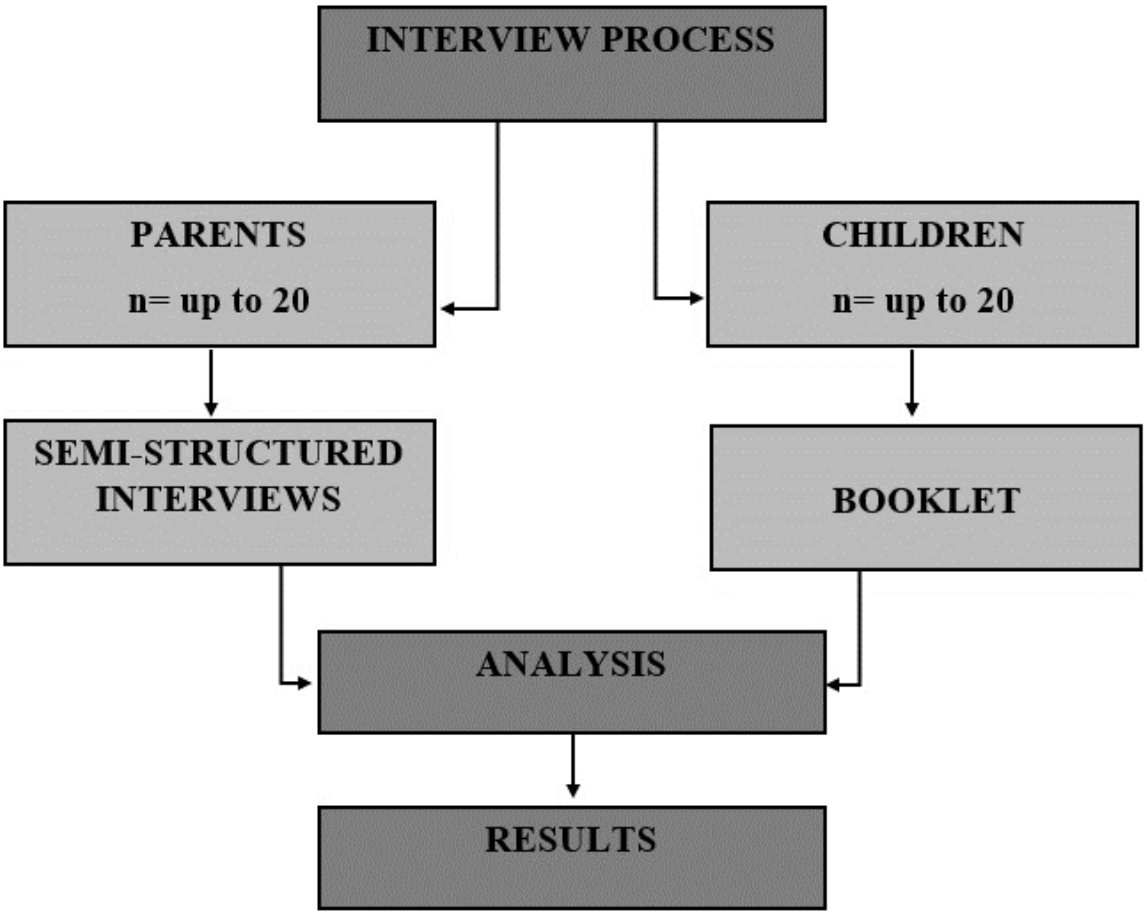

Figure 3.1. Schematic of the Interview Process.

3.4.3. Interview Format

Amongst parents a semi-structured interview will be used. Informed consent will be collected from the participants before the interview. The parent(s) of each child will be interviewed in a session that will last approximately 30 minutes. The interview will comprise a series of open-ended questions on their experiences and impact of the Perthes' disease on their everyday life. The interviews aim to collect participants' experience of the disease and the impact of Perthes' disease on their lives, evaluating the daily needs that they have to deal with. The questions will investigate areas such as impact of the disease on patients and related family, the importance of clinical

management, the impact of the disease on daily living activities and sport/recreational activities. Thus, based on this pilot work, the interview will be directed to the importance of defining key outcomes in the treatments and identifying possible outcomes in the management of Perthes' disease. In the children's group, a booklet including questions related to Perthes' disease and its influence in the child daily life, will be completed by each child, with the help of the interviewers where needed. The booklet aims to be a prompt for further discussion involving children, and it contains questions related to pain, hip mobility, related influence of the disease in the daily live activities and effects of the treatment(s), explained through the use of emoji to ensure ease of completion. The final part of the booklet includes a personal description of a recent bad day and good day experienced by the child. This last part will be transcript in children younger than 8 years old (which will be helped by the interviewers) and recorded as an open-questions interview in children older than 8 years old. The booklet completion process take no longer than 30 minutes.

Consultation with the Health Research Authority deemed this study a service evaluation project with no requirement for ethical approval (reference 60/89/81). Informed consent will be assumed if participants agree to fill in the survey. A consent form indicating informed consent will be signed by parents to agree participation in the interview, and allow voice recording of the interviews.

3.4.4. Interview Analysis

All interviews will be recorded and transcribed, and then the transcripts and the recordings will be analysed in line with the qualitative approach following the National Centre for Research Methods guidelines (Malterud, Siersma and Guassora,

2016). The process of analysis of the qualitative data will summarize and define the key outcomes based on the stakeholders' opinion.

3.5. IDENTIFICATION OF KEY OUTCOMES TO CLINICIANS

3.5.1. Overview

A Delphi survey (Smith and Firth, 2011) (figure 3.2) will be conducted to identify the key outcomes important to orthopaedic surgeons, GPs and physiotherapists. The Delphi approach is a consensus technique that involves a series of questionnaires administered to target experts in the investigated area, which answer in anonymous way in order to reduce reciprocal influences and bias (Smith and Firth, 2011).

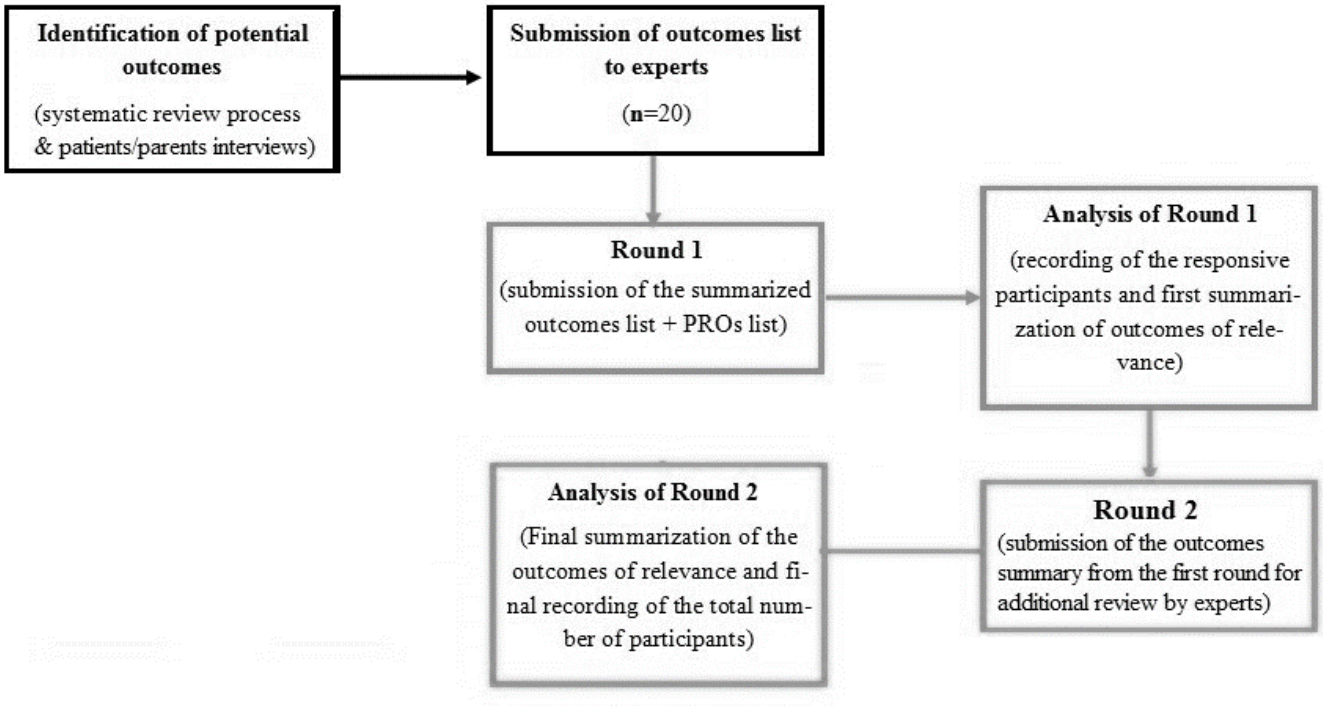

Figure 3.2. Schematic summary of Delphi Survey Process.

3.5.2. Identification of Potential Outcomes

A complete list of all the outcomes present in literature will be made following the approach of the systematic review described in this protocol. Additional outcomes will be included following the PROs obtained by the patients/parents' interviews. Each outcome will be listed both individually and by domain.

3.5.3. Participants

Previous studies have indicated that a sample size of at least 20 clinicians is adequate in order to achieve the main goals of Core Outcome studies (Hsu and Sandford, 2007). Participants will be those with experience of managing children with Perthes' disease. This group of experts will include orthopaedic surgeons, GPs and physiotherapists, including both UK experts and an overseas experts group. The clinicians involved in the study will be selected through the British Society of Children's Orthopaedic Surgery (BSCOS) and the IPSG. Participants will be contacted and invited to participate in the survey by email using a bespoke Core Outcome Set Delphi management tool.

3.5.4. Delphi Survey

The survey will be based on 2 stages (rounds). Clinicians involved in the study will have a 3 weeks time period to complete each stage of the survey.

3.5.5. Delphi Round 1

The electronic data collection form will seek details of participants' demographic data (participant name, clinical role, place of work and contacts), seek the important list of selected outcomes (from the review and the patients/parents' interviews) (to be graded on a score of 1-9 with "1-3=not relevant"; "4-6=important but not critical"; and "6-

9=extremely relevant") and will give the possibility to add additional outcomes considered of importance (and related scores) not listed in the list.

3.5.6. Analysis of Delphi Round 1

The analysis of the data will summarize the outcomes considered most important. Additional outcomes added by the clinicians will be reviewed by 2 assessors (D.G.L. and W.J.L.) in order to ensure that they do not refer to outcomes already listed. The number of the invited participants that respond to the survey will also be recorded.

3.5.7. Delphi Round 2

At the second stage, participants involved in round one of the Delphi survey will be able to see the summary of the data obtained in the round one, asking them to review again the list of outcomes, considering if the outcomes present in the summarized list have to be classified as relevant or not. Participants that do not respond to round one will be excluded in round two.

3.5.8. Analysis of Delphi Round 2

Total number of participants invited to participate and do participate in round 2 will be recorded. The distribution of scores will be summarized. In the summary of the percentage agreement, each individual outcome will be classified as "consensus in", "consensus out" or "no consensus" based on the percentage.

3.6. CONSENSUS MEETING

The final stage of the study will be based on a consensus meeting between a selected group of clinicians and a selected group of patients/parents (for a total of 24

participants, adhering the OMERACT guidelines for the consensus meeting structure (Boers et al., 2014).

Before the meeting, the patients/parents group will be able to review the outcomes selected by the clinicians during the Delphi survey, and this data will be discussed during the consensus meeting.

3.6.1. Definition of Consensus

Following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) guidelines (Schunemann and Brozek, 2008), in order to define consensus, outcomes inclusion will be indicated as the agreement by the vast majority (>70% of the group) of the "extremely relevance" (7-9 points range) of the discussed outcomes, with only a minority (<15% of the group) of participants that consider it as "not relevant" (1-3 points range). Consensus for outcomes exclusion will be indicated as the agreement by the vast majority (>70% of the group) of the "not relevance" (1-3 points range) of the discussed outcomes, with only a minority (<15% of the group) of participants that consider it as "extremely relevant" (7-9 points range).

3.7. DISCUSSION

The evaluation of literature on Perthes' disease shows a clear lack of common outcomes measures reported among different studies in the literature. This lack of a COS impacts the ability to produce meaningful research, and inhibits the ability to compare research findings in order to clearly define the management guidelines for Perthes' disease. Thus, a clear definition and implementation of a COS is required in order to help future researchers identify the primary outcome measures in their studies in order to increase the quality and the clinical application of the results obtained.

3.8. SEARCH STRATEGIES

PubMed search strategy: 1 January 1990 to 1 January 2017

1. "Femur Head Necrosis" [MeSH]
2. Osteonecrosis[MeSH]
3. (Perthe* OR Legg-Calv*-Perthe* OR Legg-Perthe* OR Calv*-Perthe*)
4. (Perthe* AND Legg-Calv*-Perthe* AND Legg-Perthe* AND Calv*-Perthe*)
5. (#1 OR #2 OR #3 OR #4) AND Hip*
6. (#5) AND (Child* OR Infant*)

Cochrane CENTRAL search strategy: 1 January 1990 to 1 January 2017

1. MeSH descriptor: [Femur Head Necrosis] explode all trees
2. MeSH descriptor: [Osteonecrosis] explode all trees
3. (TITLE-ABSTRACT-KEYWORDS) Perthe* OR Legg-Calv*-Perthe* OR Legg-Perthe* OR Calv*-Perthe*
4. (TITLE-ABSTRACT-KEYWORDS) Perthe* AND Legg-Calv*-Perthe* AND Legg-Perthe* AND Calv*-Perthe*
5. (TITLE-ABSTRACT-KEYWORDS) (#3 OR #4) AND Hip*
6. (TITLE-ABSTRACT-KEYWORDS) (#5) AND (Child* OR Infant*)

Web of Science search strategy: 1 January 1990 to 1 January 2017

1. (TOPIC) "Femur Head Necrosis"
2. (TOPIC) Osteonecrosis
3. (TOPIC) Perthe* OR Legg-Calv*-Perthe* OR Legg-Perthe* OR Calv*-Perthe
4. (TOPIC) Perthe* AND Legg-Calv*-Perthe* AND Legg-Perthe* AND Calv*-Perthe*
7. (TOPIC) (#1 OR #2 OR #3 OR #4) AND Hip*
8. (TOPIC) (#5) AND (Child* OR Infant*)

CHAPTER 4

PERSPECTIVES ON THE SOCIAL, PHYSICAL, AND EMOTIONAL IMPACT OF LIVING WITH PERTHES‘ DISEASE IN CHILDREN AND THEIR FAMILY: A MIXED METHODS STUDY

The contents of this chapter were published in: **Leo, D.G.**, Murphy, R., Gambling, T., Long, A., Jones, H. and Perry, D.C., **2019**. Perspectives on the Social, Physical, and Emotional Impact of Living with Perthes' Disease in Children and Their Family: A Mixed Methods Study. *Global Pediatric Health*, 6, p.2333794X19835235.

4.1. INTRODUCTION

Perthes' disease is an idiopathic osteonecrosis of a developing hip (Perry and Bruce, 2011; Perry and Hall, 2011), with the typical onset between 4 and 8 years old, and a predominance in males (4:1 male-female ratio) (Perry and Bruce, 2011; Perry and Hall, 2011). The incidence of Perthes' disease is greatest in White children from North Europe, particularly the Northern Part of the UK and Norway (Wiig, 2009; Perry et al., 2012a; Perry et al., 2012d). The management of the disease varies between surgical interventions (i.e. typically Varus osteotomy or Salter's osteotomy) and conservative approaches (i.e. physiotherapy, bracing, bed rest) (Hefti and Clarke, 2007; Leroux, Abu Amara and Lechevallier, 2018). There is little high quality evidence pertaining to treatment of Perthes' disease (Hefti and Clarke, 2007; Leroux, Abu Amara and Lechevallier, 2018). The main aim of existing treatment is to regulate the collapse of the femoral head through 'containment', and to manage the pain (Onishi, Ikeda and Ueo, 2011; Moghadam, Moradi and Omidi-Kashani, 2013; Leroux, Abu Amara and Lechevallier, 2018).

Typically, the commonly reported outcomes of Perthes' disease are radiographic, in particular the shape and congruency of the femoral head (Stulberg et al., 1991; Leroux, Abu Amara and Lechevallier, 2018). The profound effects that Perthes' disease has on the lives of affected children and their families, has not been explored in the literature. The treatment uncertainties and absence of national or international consensus has a marked effect on increasing the anxiety of families. Whilst child-specific quality of life questionnaires have been used in affected children (Hailer, Haag and Nilsson, 2014; Palmen et al., 2014a; Matos et al., 2018), it is unclear if these capture the outcomes that are most important to the children and their family. Moreover, previous studies that have investigated quality of life in children with chronic illness have

shown how the disease/condition negatively impacts social functions and school attendance, as well as influence parent behavior towards the child (Emerson et al., 2016). No prior study has performed an in depth investigation to understand the physical, emotional and social impact on quality of life in children with Perthes' disease, and the impact that this may have on their family. This information would highlight the importance of well-being of these children and their families to clinicians responsible for diagnosis and treatment of the disease in order to improve the clinical management of the disease inside and outside the hospital care.

4.2. PATIENTS AND METHODS

4.2.1. Participants

A concurrent triangulation mixed methods study was designed, including 18 parents and 12 children (2 girls and 10 boys), with an age ranged between 4 to 12 years (mean 7.1 years, SD±4.1 years) at the time of the interview (Table 4.1). Participants engaged in this study were from Alder Hey Children's Hospital Liverpool (UK), between June and August 2017. Participants were patients approached during routine visits, by verbal approach and additional patient information sheet. Inclusion into the study was a diagnosis of Perthes' disease in the child (irrespective of the current stage of disease or method of treatment), below the age of 16 years, willing to participate in the interview process and the ability to be conversant in English.

Table 4.1. Patient's demographic data.

Patient Number	Sex	Age (years)	Parent(s) Interviewed
1	M	9	M & F
2	F	5	M & F
3	M	12	M
4	M	5	F
5	M	6	M & F
6	M	5	M
7	M	4	M & F
8	M	8	M
9	F	6	M & F
10	M	12	M
11	M	5	M
12	M	8	M
13 *	M	5	M

M= Mother and F= Father

**for this child, only the parent's interview data is available.*

Consultation with the Health Research Authority deemed this study a service evaluation project to determine important outcomes related to standard care (reference 60/89/81). A signed consent form was collected from parents who agreed to participate seeking their permission for the interview to be recorded and analysed in an anonymised format.

4.2.2. Data Collection

The data collection process included two stages: 1) children completed a bespoke questionnaire 2) parents engaged in a semi-structured interview. The questionnaire (Appendix A) was completed first by the child, followed by the interview with the parent(s) (Appendix B) in a session that lasted ~30 minutes. The completion of the booklets and parent interviews were conducted in the Orthopaedic Unit of Alder Hey Children's Hospital Liverpool (UK), following a routine clinical appointment for Perthes' disease. Informed consent was collected from participants to record the interview.

The questionnaire sought to score different situations of daily life in both good and bad days, which was completed with prompts from the interviewer (as required). The questionnaire contained questions related to social, physical and emotional impact of Perthes' disease (such as pain, the impact of the disease on social relationships, and the influences of it on daily life activities). Responses were collected through the use of emoji's to ensure ease of completion. The questionnaire completion process took no longer than 30 minutes. The questionnaire was designed (AFL, TG) with the help of two families affected by Perthes' disease, to ensure that it was sufficient to extract relevant information. It was specifically designed to be young child-friendly, easy and fun to complete by a young child. Phrasing of particular items were modified as additional data were collected, in order to ease interpretation and provide a clear meaning to the child.

The interviews aimed to explore participants' experience of the disease, and the impact of Perthes' disease on their lives. The questions investigated areas such as impact of the disease on patients and related family, the importance of clinical management, the

impact of the disease on daily living activities and sport/recreational activities. The interview began with open questions to seek a general picture of the child´s life, obtain information about the current stage of the disease and determine general information related to the family of the child (such as: "Can you tell me when you started to realise that something was going on with your child?" or "Can you tell me some information about your family, such as how many people there are and if he/she has any siblings?"). Then, the interview continued with a series of open-ended questions on their experiences and impact of Perthes' disease on their everyday life.

The design of more specific and detailed questionnaire and interview for Perthes' disease aimed to seek a better understanding of the limitations related to this specific condition, which are usually assessed with tools that are not specific for Perthes' disease (i.e. KIDSCREEN-10; EQ-5D-3L: PedsQL 4.0) (Hailer, Haag and Nilsson, 2014; Palmen et al., 2014a; Emerson et al., 2016).

Both the children's questionnaire and the parents' interview were designed conducted and analyzed by members of the team with background/training in psychology/qualitative research (DGL, RM, AL, and TG).

4.2.3. Children's Questionnaire Analysis

The questionnaire aimed to capture a general overview of living with Perthes' disease through the children perspective, and to understand the impact that the disease has on the children's daily living activities. The main questionnaire's outcome was the difference in daily life activities and pain between good and bad days.

The ‘emoji scores’ of the children’s questionnaire were analysed using a quantitative approach (score of one was related to the “happiest” emoji and five to the “saddest” emoji).

A Shapiro-Wilk test was used to ensure residuals were normally distributed ($p>0.05$) and it was found a moderate correlation of the dependent variables with a Pearson Correlation Test ($0.3< | r | <0 .5$). This data was analyzing using a MANOVA (IBM SPSS software, v.22.0) looking for statistical significance ($P<0.05$).

4.2.4. Parents’ interviews analysis

The obtained sample size of 18 parents and 12 children was enough to reach saturation of ideas for the purpose of this study. Interviews were digitally recorded, transcribed and uploaded to QSR NVivo Software, v.2.0. Data were processed through a six-stage model (Braun and Clarke, 2006). Multiple reading of transcripts and listening to audio files was undertaken in order to achieve immersion into the data. Transcripts were coded line-by-line, identifying themes in accordance with the overall aims of the paper (Sparkes and Smith, 2014). The themes defined were reviewed by four researchers (D.G.L., R.M., A.L. and T.G.) and used to code the related frameworks, which some of the codes moved to other themes and non-relevant data removed from the analysis.

4.3. RESULTS

4.3.1. Children’s Questionnaire

It were identified 8 characteristics related to good and bad days (Figure 4.1): *1) presence/absence of pain; 2) use of painkillers; 3) limitations in doing things; 4)*

limitations in play activities; 5) limitations in going to school; 6) ability to sleep; 7) feel sad; 8) feel feed up.

Data are displayed in Table 4.2. Patients' characteristics are displayed in Table 1. Among the 8 characteristics, only the "limitations in going to school" did not show statistical significance ($P<0.05$) between good and bad days.

Table 4.2. Children's booklet analysis.

Characteristics	Good Days	Bad Days	p-value
Presence/absence of pain	range (1-3)	range (3-5)	0.003
Use of painkillers	range (1-3)	range (3-5)	0.024
Limitations in doing things	range (1-3)	range (3-5)	0.014
Limitations in play activities	range (1-3)	range (3-5)	0.004
Limitations in going to school	range (1-3)	range (3-5)	0.071
Ability to sleep	range (1-3)	range (3-5)	0.006
Feel sad	range (1-3)	range (3-5)	0.002
Feel feed up	range (1-3)	range (3-5)	0.002

range( ) = emoji scores on the children booklet; where 1 is the happiest emoji and 5 is the saddest emoji.

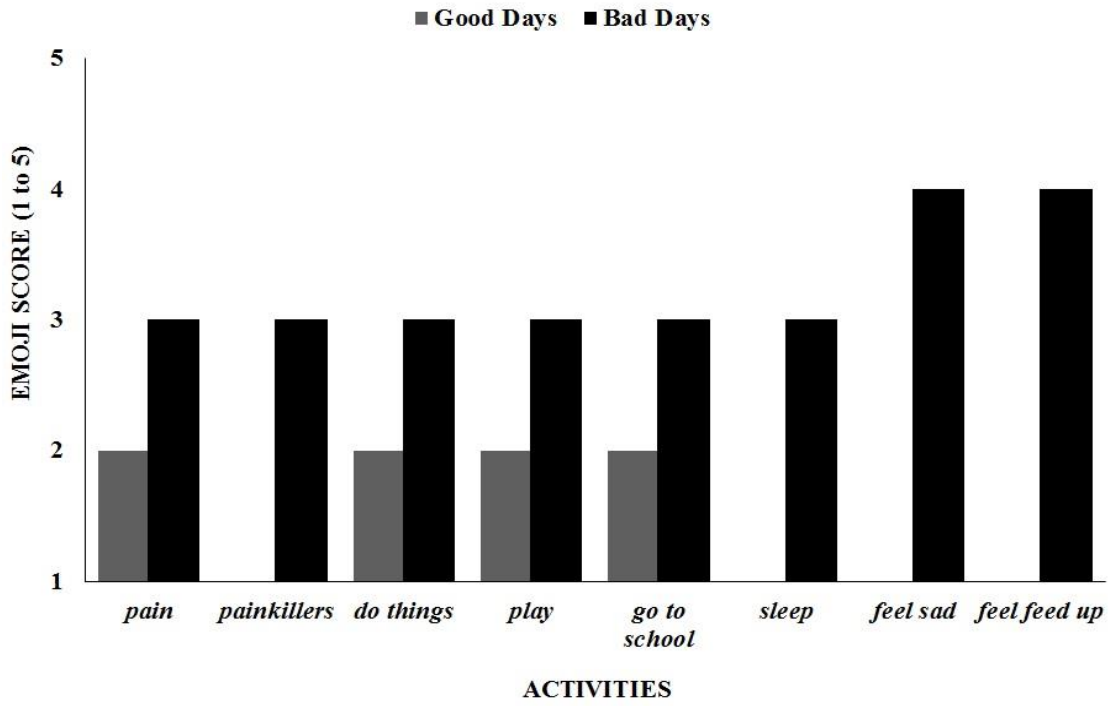

Figure 4.1. Comparison between Good and Bad days.

4.3.2. Parents' Interviews

Themes that emerged from analysis of the parents´ interviews are represented in this section using verbatim quotes to highlight the participants' perspective. Four key themes emerged with a number of second order contained within the key theme:

1. **Family Perspectives and General Impact on Family Life**

Lack of Awareness

Parents were unaware of Perthes' disease prior to diagnosis. They also reported difficulties in obtaining an accurate diagnosis in the early manifestation of the disease from the healthcare professionals they contacted.

> *"In the beginning, we were very worried and scared, because we did not know the disease and there were not much information we could access until we got*

the right channels. Different people were saying different things and we were stressed and scared about this." (Patient 2, Mother)

The lack of information about the disease made the parents afraid because they could not find a good source of information and had no idea how to manage their child and the disease.

Additionally, parents felt frustrated with health care professionals in the time it took to reach a diagnosis. Perthes' disease was often not recognised by general practitioners due to its infrequency and non-specific initial manifestations, which can be mistaken for other non-serious conditions (i.e. growing pains).

"Before it was diagnosed it was a nightmare, nobody could say what it was, because nobody knew what was going on. And they were continuing to say that was a growing pain." (Patient 6, Father)

Siblings Jealousy

The relationship with siblings often affected family life. Parents felt they tended to prioritise the affected child and believed that other siblings started to feel less loved and ask for more attention.

"It impacted even his sister, because she was feeling that all the attention was for her brother and she got a little upset about this." (Patient 1, Mother)

Jealousy seemed to have a greater impact amongst younger siblings (less than 10 years old), yet older siblings seems to exhibit a protective behavior toward their sick younger sibling:

"His sister is older, so she feels quite responsible for him and takes care of him."

Parental Concerns for the Child's Future

Parents were often concerned about how Perthes' disease may affect their child in the long-term. Usually the concern was related to the possibility of a hip replacement in the near future, or the limitations that may be placed upon pursuing a normal life:

> *"We are afraid she cannot do what she wants to do. Like any parents, we wish she can do whatever she wants, like do sport if she wants, or other normal things." (Patient 2, Father)*

Parents were often frustrated about their child's condition, and felt powerless about a condition that was difficult to manage:

> *"It was just me carrying him around all the time for all the day. His dad and I, carrying him to the toilet, carrying him to the school." (Patient 5, Mother)*

Parental Work

Parents often reported that they had to change or quit their job in order to manage the disease, which may have significant influence on the financial status of the family.

> *"I had to quit my job to follow him, and now I am doing just local work because it is easier to manage." (Patient 1, Mother)*

> *"As a single parent, I had to quit my job to take care of her." (Patient 9, Mother)*

2. Impact of Perthes' disease on Activities of Daily Living

This theme describes the impact that Perthes' disease had on the daily life of patients and their family, such as changes in daily schedules, problems related to getting

dressed unaided or school attendance and participation in physical education or other activities. This theme has been divided into five "second order themes": *1) Limitations imposed by parents; 2) Impact on walking; 3) Feeling of pain; 4) Poor sleep quality; 5) Impact on school.*

Limitations Imposed by Parents

Limitations and restrictions were often imposed by parents (sometimes following the advice of medical professionals) fearful of worsening the symptoms, or worsening the disease.

> *"We decided to limit her in some activities because we were afraid she could get injured." (Patient 2, Father)*

Parents also described feelings of disappointment with the limitations imposed upon their child:

> *"She knows she cannot do some stuff that other children do (like jump), and she gets upset and sometimes she does not want to go to other children's parties." (Patient 9, Mother)*

Children that were very active and involved in sporting clubs were restricted:

> *"He is a very good gymnast and dreams to go to the Olympics, but he had to stop his sport for now." (Patient 3, Mother)*

Children were held back from enjoying their social time with their peers. This was a particularly important issue for younger children because they lacked the comprehension to understand why they could not do some of the same activities as their friends:

"*One of the problems is stopping him from playing outdoor games with his friends. It is difficult for him understand that he has to avoid jumping around or play on trampolines." (Patient 6, Mother)*

Impact on Walking

The impact of the disease on walking typically related to a limp, which was reported to affect most of the children:

"He has a constant limp." (Patient 3, Mother)

This did not allow them to walk long distances or climb stairs, due to pain and tiredness.

Feeling of Pain

Children with Perthes' disease often reported pain, especially after long walks or long periods of outdoor activities. The pain was often localized to the knee with some exceptions, where the pain affected the whole leg. It was infrequent for parents to identify the pain localizing to the hip.

"The pain is mainly in his knee." (Patient 4, Father)

Often, children decided to "deny the pain" or avoid the topic with their parents in order to be permitted to carry on with the activity they were doing in that moment:

"I think he is in pain for most of the time, but because he has a high pain threshold, he does not let me know it really. But I think he is in pain a lot, for most of the time, and he has just learned how to deal with it." (Patient 3, Mother)

Poor Sleep Quality

Often the pain seemed to be intensified during the night. Children with Perthes' disease reported poor sleep and needed support during the night from their parents when going to the toilet, or needed emotional support related to managing the pain. They often required painkillers to help them sleep.

> *"During the night, we were using morphine to reduce his pain, and let him spend time in the bath, because these were the only ways we could help him." (Patient 1, Mother)*

Impact on School

The impact on school was related to long absences due to pain, preparation and recovery from surgery, and the follow-up visits to healthcare practitioners:

> *"He missed a lot of school, especially due to the pain. We had a teacher come to our house to help him continue studies during the 12 months after surgery." (Patient 1, Mother)*

School absences affected their learning and often parents had to find solutions such as home tutoring from a private teacher during the recovery period.

Additionally, the physical conditions (limping, pain) and the limitations imposed, resulted in the children missing Physical Education (PE), which reduced their daily activity levels:

> *"He had to skip PE at school." (Patient 3, Mother)*

3. Emotional Impact of Perthes' disease

Perthes' disease had a strong emotional impact on both children and their family. Broadly, families could be divided into those that were "accepting of the disease" and those that were "not-accepting of the disease".

Those that accepted the disease typically continued with life without letting the disease stop them:

> *"He does not show me that he is upset or scared by the disease, but I think he is. It is just that his resilience is high." (Patient 3, Mother)*

Those that did not accept the disease had greater frustration about their condition with more concern about the long-term implications. This group tended to be formed of older children (7- 8 years old and over):

> *"I think he is a little bit sad about his condition. He does not say very much about it. I think he is a little bit worried about the operation and I think he wants just get over it as soon as possible." (Patient 13, Mother)*

Younger children (under 8 years of age) appeared less able to comprehend their situation, yet demonstrated a general sadness related activity restriction, without a real concern related to their health condition.

4. Perthes' Disease and Social Relationship

Although Perthes' disease impacted the daily life of patients and family in many ways, a positive response seemed to come from social relationships with other children. Affected children seemed generally well supported by their peers:

> *"His friends are very supportive. In his class, there are many girls that take care of him, helping him moving around with the wheelchair. And they*

continue to involve him in all their games and continue to come visit him at home." (Patient 1, Mother)

The support of their peers was fundamental in order to let patients manage the emotional aspect of their condition in the best way possible. In addition, the parents reported how they felt supported by the family of other children and how they tried to provide help in the managing of the disease:

"The parents of his friends are very supportive too. A couple of weeks ago we had a day out with other parents, and there was a trampoline, and the other parents were saying to their children to not go on it because [my child] could not go on it. So, they were stopping their own children so that he did not feel excluded from the games."(Patient 6, Father)

4.4. DISCUSSION

This study aimed to explore the social, physical and emotional impact of Perthes' disease on affected children and their families. The study shows for the first time an in-depth insight into the profound effects of this disease, beyond simply a self-limiting condition affecting the immature hip. Perthes' disease significantly impacts daily life with experience of pain; inhibiting play and activities; limiting school attendance and interfering with sleep. These factors negatively affect the social, physical and emotional quality of life of the affected child and their wider family.

Impact on the children: For the child's perspective, Perthes' disease affects children's everyday life on both good and bad days. Pain is often the characteristic that limits most of the child's ability to participate in normal daily activities such as playing outside or climbing the stairs on the bad days and reducing the quality of sleep, which

increases the tiredness of the children during the day and negatively influences their mood. Similarly, to other children with chronic illness Perthes' disease limits everyday tasks playing and attending school, but it also shows Perthes' disease has an emotional impact causing sadness and unhappiness especially when the child felt activity had been limited.

From the parent perspective there were similarities particular emphasis was around pain and sleep. School attendance and restrictions on activities (e.g. physical education) were also an issue that caused considerable frustration. It is well-established that hospitalization in children with chronic diseases has a negative impact of child quality of life related to school absence (Ramsey et al., 2001; Sehlo and Kamfar, 2015). Nevertheless, whilst parents understood that the restrictions were necessary they felt more advice/guidance on physical activity was warranted as there is currently inconsistency in the information available to them.

Impact on the parents and siblings: The findings from the current study suggest that the disease affects the wider family (parents and siblings), emotionally, in similar way to that of affected children. Socially, parents have to change their daily schedule and modify their life in order to deal with the disease, which is a similar finding to other studies of childhood conditions (Ramsey et al., 2001; Goldbeck and Melches, 2005; Fleary and Heffer, 2013; Malheiros et al., 2015; Sehlo and Kamfar, 2015). These data provide more in-sight and suggests that parents feel powerless in the management of the disease and demonstrate frustration with the limited amount of medical understanding of causes and treatments of Perthes' disease. The lack of confidence in the clinical management often begins with diagnosis; clinicians generally misdiagnose Perthes' disease in the early stages, which results in delayed diagnosis and also adverse impact on the child's quality of life causing anxiety and worry for the parents. The

paucity of and inconsistencies in available information causes uncertainty about the clinical management and constant fear that the treatment is correct, which leaves parents disappointed and lacking assurances. Seeking and taking heed of parents' views, and the impact they have on the wider family is highly relevant for clinicians managing this condition.

Limitations. The study has been able to capture the views of parents of children with Perthes' disease during at different stages of treatment/healing process supporting the data with the additional feedback of the children (through the children's questionnaire), which is a strength of the study, although the study only included patients from a single centre, which induces limitations related to a small sample size and poor patients' diversity. At the outset, the study intended to seek also a personal view from children through a personal narrative in the questionnaire, but most children were too young to complete this without the help of parents, which gave a strong influence on their child's narrative. Nevertheless, the children's questionnaire has shown useful insight into the level of particular symptoms and concerns through the use of emojis.

The study demonstrate the social, physical and emotional impact of Perthes' disease, on the life of the child and related family. Perthes' disease is a profound childhood disability, with little high quality evidence pertaining to its treatment nor national or international consensus. These findings add in-depth insight into the challenges caused by this disease for health care professionals involved in clinical management. Co-ordinated multicenter high-quality research is needed to improve the understanding of the disease, giving consideration to non-radiographic outcomes. The themes emerging from this qualitative analysis will be used to inform the development of a Core Outcome Set (Chapter 3) for use in clinical research, and routine care.

CHAPTER 5

THE OUTCOMES OF PERTHES' (TOP) STUDY

DEVELOPMENT OF A CORE OUTCOMES SET FOR CLINICAL TRIALS IN PERTHES' DISEASE

5.1. INTRODUCTION

Perthes' disease (also known as Legg-Calvé-Perthes disease) is an idiopathic osteonecrosis of the femoral head in children (Perry and Bruce, 2011; Perry et al., 2012a). It is unclear what causes the disease, although socio-economic deprivation has been demonstrated to be the primary risk factor (Perry and Hall, 2011; Perry et al., 2012d). Perthes' disease occurs five times more in boys than in girls, with a greatest incidence amongst white children in the UK and North Europe (Wiig, 2009; Perry and Hall, 2011; Perry et al., 2012a; Perry et al., 2012d). Symptoms of the disease include limping, stiffness of the hip joint and pain. Typical onset is between the ages of 4 and 8 years (Perry and Bruce, 2011; Perry and Hall, 2011).

Clinical management of Perthes' disease focuses on the prevention of the femoral head collapse and functional recovery (recovery of hip motion; reduction of pain) (Onishi, Ikeda and Ueo, 2011; Moghadam, Moradi and Omidi-Kashani, 2013). Treatment approaches vary between surgical interventions (e.g. varus or shelf osteotomy) and non-surgical interventions (e.g. bed rest or wheelchair), but importantly the management guidelines differ between countries, between hospitals and even among surgeons within the same hospital (Hefti and Clarke, 2007). The debate on which treatment gives the best outcomes is ongoing, and divergent opinions on Perthes' disease management in the paediatric orthopaedic community have been, in part, borne out through the absence of standardised outcomes (Chapter 3).

Core Outcomes Sets represent consensus-derived minimum sets of outcomes to be reported in studies investigating a specific condition (Boers et al., 2014; COMET-Initiative, 2018). By establishing a minimum set of outcomes to measure and record in research studies and clinical trials, this will enable comparisons to be made between

studies, and facilitate meaningful meta-analyses (Boers et al., 2014). The use of COS is well-established through clinical research, though their adoption is somewhat slower in orthopaedic surgery.

The aim of this study was to identify, using the COMET-Initiative guidelines, a suite of key physical, emotional and social outcomes to be employed in clinical practice and research into Perthes' disease.

5.2. METHODS

5.2.1. Systematic Review

It was searched the Cochrane Library, PubMed and Web of Science databases to identify manuscripts related to the management of Perthes' disease, with either operative or non-operative interventions, between January 1990 and January 2017 using the search strategy outlined in the study protocol in chapter 3. All randomised controlled studies, cohort studies and case series that included patients treated for Perthes' disease, irrespective of their treatment type, that reported childhood outcomes of the disease, were included. Inclusion criteria were established following the PICO approach: 1) Population: children with Perthes' disease; 2) Intervention and 3) Comparator: any treatment; 4) Outcomes: any outcome. Only manuscripts written in English language were included. Study eligibility was assessed by two independent reviewers (D.G.L. and W.Y.L.) who screened all the titles and abstract using Rayyan software (Ouzzani et al., 2016). The full text article was obtained for all manuscripts fulfilling the inclusion criteria. Data from all eligible studies were extracted as detailed in the study protocol in chapter 3, which involved identification of the primary objective of the study, prospective/retrospective data collection, study type,

population, number of patients, conservative management, surgical management, primary and secondary outcomes measured, outcomes assessment tools and follow-up. All outcomes obtained were categorised into 1 of the 5 domains of the OMERACT filter 2.0 (Boers et al., 2014), which includes the areas that should be covered by outcomes measures in order to ensure an adequate reporting of the results. Domains were divided in: 1) adverse event; 2) life impact; 3) resource use; 4) pathophysiological manifestations; and 5) death. A sixth domain of "technical consideration", suggested by Dorman et al. (2018), not present in the original OMERACT filter, was also included.

5.2.2. Qualitative Interviews

Qualitative interviews were held with parents and children to identify the key outcomes of Perthes' disease amongst families. The methods and in-depth outcomes are reported in chapter 4.

5.2.3. Delphi Survey

The list of outcomes obtained from the systematic review and qualitative interviews were combined in a Delphi Survey to identify the core outcomes important to key stakeholders. Stakeholders included orthopaedic surgeons, patients and parents with invites targeted to groups around the world. The Delphi Survey involved two stages (rounds), each lasting 3 weeks. The first round of the survey collected participants' demographic data (participant name, stakeholder group, country), and asked the participants to score the list of suggested outcomes (between a score of 1-9, where "1-3=not relevant"; "4-6=important but not critical"; "7-9=extremely relevant"). As part of the first round, participants were also given the opportunity to suggest additional important outcomes not otherwise identified. The data obtained from round 1 were

then analysed using bar charts stratified by stakeholder group. A second survey (round 2) was then conducted presenting the graphical output of each outcome by stakeholder group, with additional outcomes also added. Participants were invited to score again the outcomes using the same descriptors. Data obtained from round 2 were then summarised using the GRADE guidelines (Balshem et al., 2011) as "consensus in", "consensus out" or "no consensus". "Consensus in" was defined as the agreement of the vast majority (>70% of the group) on considering the outcome extremely relevant (7-9 points range), with only a minority (<15% of the group) considering the outcome not relevant (1-3 points range). "Consensus out" was defined as the agreement of the vast majority (>70% of the group) on considering the outcome not relevant (1-3 points range), with only a minority (<15% of the group) considering the outcome extremely relevant (7-9 points range).

5.2.4. International Involvement

The summary of data from both rounds of the Delphi survey was presented to 20 international surgeons at the International Perthes Study Group meeting in Dallas in October 2018, to seek additional feedback from this expert group. Participants were given the opportunity to discuss the Delphi survey results and put forward any comments for discussion at the final consensus meeting.

5.2.5. Final Consensus meeting

The list of outcomes obtained from the Delphi Survey and the additional feedback obtained from the IPSG were taken to a consensus meeting in January 2019. There were 10 participants: 3 international surgeon representatives; 3 international parents/patients' representatives; a physiotherapist; 2 of the researchers involved in the study; and an external chair (who did not participate in the voting procedure).

First, the full list of 38 outcomes included in the Delphi survey were presented, with outcomes split according to if they were “consensus in”; “consensus out”; or “no consensus”. There was the opportunity for open discussion related to all outcomes, with any comments from the IPSG made available to the group. Participants asked to anonymously score each outcome, using an online platform (VoxVote (VoxVote, 2019)), to ascertain those to include in the final COS.

5.3. RESULTS

5.3.1. Systematic Review

709 papers were identified from preliminary database searches. After additional title and abstract screening, 552 papers were excluded which were not pertinent to Perthes’ disease; were duplicates; or which did not report outcomes following an intervention. Of the remaining 157, it was not possible to access the full text of 45 papers. Outcomes were sought from 112 papers. Figure 3.1 shows the PRISMA flow diagram of the papers identification process. After data extraction 23 individual outcome domains were identified, and categorised according to the OMERACT modified filter domains (Table 5.1).

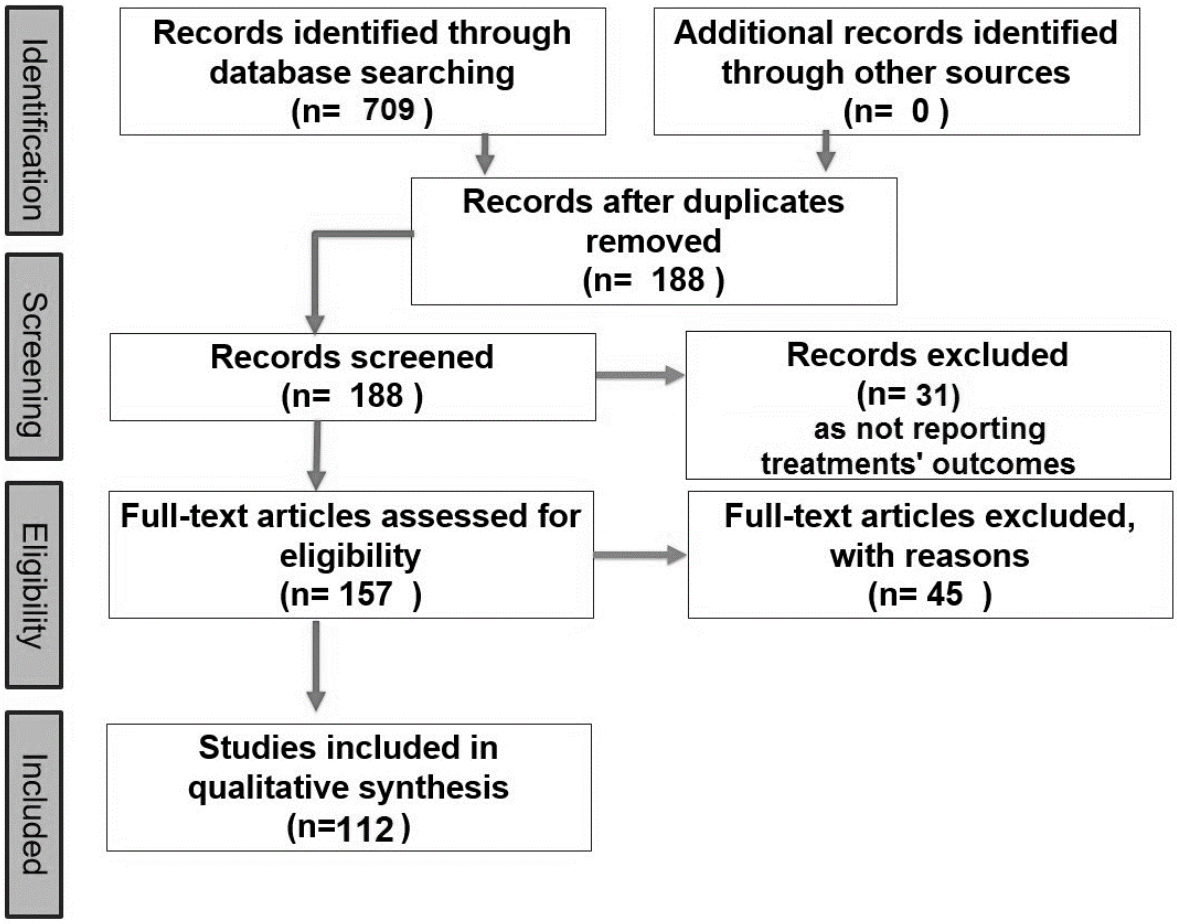

Figure 5.1. PRISMA flow-diagram showing papers identification and inclusion process.

Table 5.1. Systematic review outcomes categorised in domains (OMERACT modified filter).

Core Area	Core Domains	Outcomes
Adverse events	Adverse Events	Deformity
Life impact	Physical/Social/Emotional/ Cognitive/Health Related Quality of Life	Pain; activity of daily living; walking distance; use of walking aids; sit comfortably; pick up objects from the floor; climb stairs
Resource use	Economic/Hospital/Need for intervention/Social burden	NONE
Pathophysiological manifestations	Musculoskeletal	Trendelenburg sign; gait analysis; uneven legs length; muscle strength; hip mobility
Death	N/A	N/A
Technical considerations	Technical/Surgical considerations	Acetabular coverage; acetabular shape; articulo-trochanteric distance; broken

	Shenton's line; cartilaginous radii; evidence of arthritic changes; femoral head shape; neck shaft angle; overgrowth of great trochanter; stage of the disease

5.3.2. Patients Reported Outcomes

10 outcomes not identified through the systematic review process were identified from qualitative interviews with parents reported in chapter 4 and added. The full list of the PROs obtained is reported in Table 5.2.

Table 5.2. PROs reported by patients and parents interviews.

Core Area	Core Domains	Outcomes
Adverse events	Adverse Events	Complications of treatment
Life impact	Physical/Social/Emotional/ Cognitive/Health Related Quality of Life	Limping, family finance; quality of life; school/pre-school attendance; sleep quality; impact on sport participation
Resource use	Economic/Hospital/Need for intervention/Social burden	Length of hospital stay; requirement for further surgery; skin problems

5.3.3. Delphi Survey

Round 1 of the Delphi included a total of 162 participants, with 27% surgeons (n=44); 56% parents (n=91); and 17% affected individuals (n=27). The majority of participants were from the UK (49%, n=79) with significant representation from the USA (28%, n=46), and with a large spread of 12 other countries also represented (23%, n=37). In round 2, 62 participants (38% of round 1) did not respond to the second round of the survey despite prompts. The final number of participants' in round 2 was 100, including 36 surgeons (36% of the total participants); 46 parents (46%), and 18 affected individuals (18%) (Figure 3.2). Attendance in round 2 involved equal participation from the UK and USA, with UK 40% (n=40) of the total participants,

and USA 40% (n=40) of the total participants. The remaining 20% (n=20) of participants were from 12 other countries (Figure 3.3). The total participants' attendance of round 2 was 62% of round 1.

Table 5.3 shows the full list of the 33 outcomes reported in the round 1 of the Delphi survey, categorised into the 6 domains of the modified OMERACT filter. Five additional outcomes were suggested after round 1 (Table 5.4) and included in round 2. Of the final 38 outcomes, 16 obtained "consensus in", 22 obtained "no consensus", and none obtained "consensus out" after round 2. Table 5.5 shows the final list of the 16 outcomes that reached "consensus in" after the two rounds of the Delphi survey.

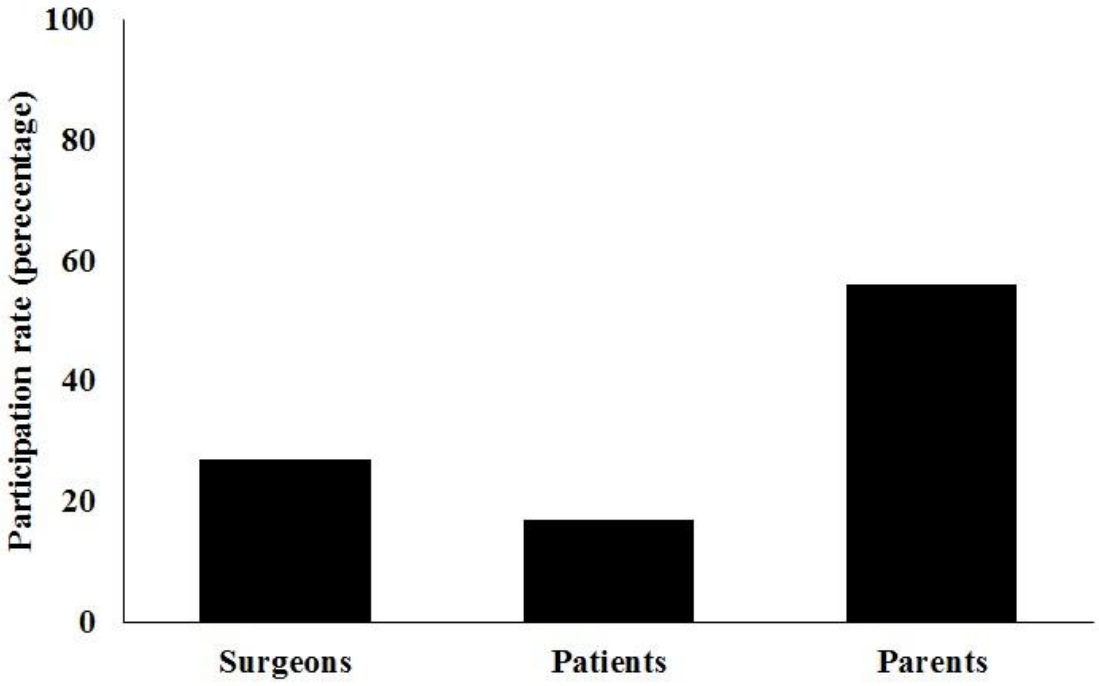

Figure 5.2. Participants' distribution Delphi round 2.

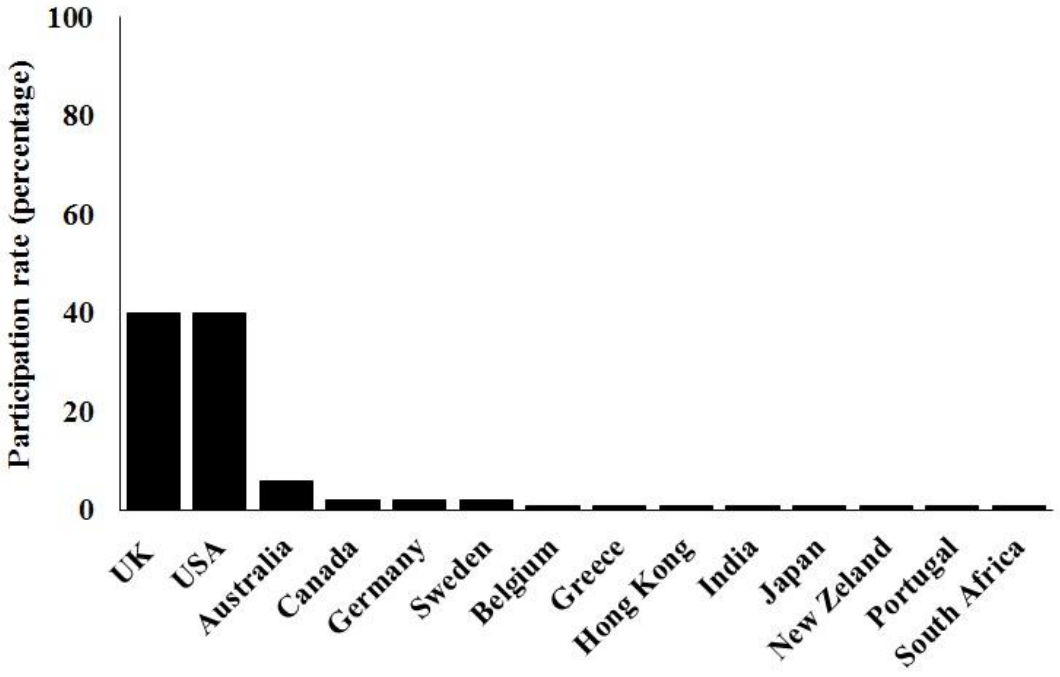

Figure 5.3. Round 2 Delphi survey participants' demographic data.

Table 5.3. Delphi outcomes list.

Core Area	Core Domains	Outcomes
Adverse events	Adverse Events	Deformity; complications of treatment*
Life impact	Physical/Social/Emotional/ Cognitive/Health Related Quality of Life	Pain; activity of daily living; walking distance; use of walking aids; sit comfortably; pick up objects from the floor; climb stairs; family finance*; quality of life*; school/pre-school attendance*; sleep quality*; impact on sport participation*
Resource use	Economic/Hospital/Need for intervention/Social burden	Length of hospital stay*; requirement for further surgery*; skin problems*;
Pathophysiological manifestations	Musculoskeletal	Trendelenburg sign; gait analysis; uneven legs length ; muscle strength; hip mobility
Death	N/A	N/A

Technical considerations	Technical/Surgical considerations	Acetabular coverage; acetabular shape; articulo-trochanteric distance; broken Shenton's line; cartilaginous radii; evidence of arthritic changes; femoral head shape; neck shaft angle; overgrowth of great trochanter; stage of the disease

* patients' reported outcomes obtained from the parents and children interviews.

Table 5.4. Additional suggested outcomes after round 1 of the Delphi.

Core Area	Core Domains	Outcomes
Life impact	Physical/Social/Emotional/ Cognitive/Health Related Quality of Life	Family Life; Psychological Impact; weight gain
Technical considerations	Technical/Surgical considerations	Time of re-ossification; hip congruency

Table 5.5. List of the outcomes that obtained "consensus in" after round 2 of the Delphi.

Core Area	Core Domains	Outcomes
Adverse events	Adverse Events	Deformity; complications of treatment
Life impact	Physical/Social/Emotional/ Cognitive/Health Related Quality of Life	Pain; activity of daily living; sit comfortably; quality of life; family life; Limping; psychological impact; school attendance; sleep quality; walking distance
Resource use	Economic/Hospital/Need for intervention/Social burden	NONE
Pathophysiological manifestations	Musculoskeletal	NONE
Death	N/A	N/A
Technical considerations	Technical/Surgical considerations	Acetabular coverage; evidence of arthritic changes; femoral head shape; hip congruency

5.3.4. IPSG Meeting Feedback

During the IPSG meeting, all the 38 outcomes included in the Delphi were discussed, along with the results from the Delphi survey. Special focus was given to outcomes that were defined as "no consensus" during the two rounds of the Delphi process. Of these outcomes, 5 were considered to warrant particular discussion in the final consensus meeting (Table 5.6).

Table 5.6. Outcomes for further discussion following IPSG feedback.

Core Area	Core Domains	Outcomes
Life impact	Physical/Social/Emotional/ Cognitive/Health Related Quality of Life	impact on sport participation
Resource use	Economic/Hospital/Need for intervention/Social burden	requirement for further surgery
Pathophysiological manifestations	Musculoskeletal	hip mobility
Technical considerations	Technical/Surgical considerations	articulo-trochanteric distance; overgrowth of great trochanter

5.3.5. Final Consensus Meeting

Domain "Life Impact" - Nine outcomes reached "consensus in" during the Delphi Survey, three (sit comfortably; walking distance; and limping) were considered

important but voted “out” as it was perceived these outcomes were broadly encapsulated within “activities of daily living”. Sport participation did not reach consensus but was suggested for further discussion by IPSG, and subsequently voted “in”. Three outcomes were added by participants during round 1 of the Delphi (weight gain; ability to climb stairs; use of walking aids), though did not reach consensus, and were subsequently voted “out”. All other outcomes of the domain “Life Impact” that did not reach consensus were voted “out” and excluded from the final COS.

Domain “Adverse Events” - Two outcomes reached “consensus in” during the Delphi survey. Of these, “deformity” was voted “out” at the consensus meeting because participants were unclear about which element of deformity was to be recorded. The outcomes of this domain that did not reach consensus during the Delphi were voted “out” of the final COS.

Domain “Technical Considerations” - Four outcomes reached “consensus in” during the Delphi survey, and were voted “in” at the consensus meeting to be included in the final COS. The consensus group considered “Acetabular congruency” and “hip congruency” a single domain and combined them as a single outcome. Two outcomes did not reach consensus during the Delphi Survey but were suggested for further discussion by IPSG (overgrowth of great trochanter; articulo-trochanteric distance), but were voted “out” and excluded from the final COS. Other outcomes were voted “out” of the final COS.

Domain “Resource Use” - The outcome “requirement for further surgery” did not reach consensus during the Delphi survey but was suggested for further discussion by IPSG, was voted “in” and was included in the final COS. Other outcomes were voted “out” of the final COS.

Domain “Pathophysiological Manifestation” - “Hip mobility” did not reach consensus during the Delphi Survey but was suggested for further discussion by IPSG, and was voted “in” by the consensus group. Other outcomes were voted “out” of the final COS.

In total 38 outcomes were presented to the consensus group and 14 outcomes were included in the final COS list (Table 5.7).

Table 5.7. List of the outcomes that reached "consensus in" to be included in the COS.

Core Area	Core Domains	Outcomes
Adverse events	Adverse Events	complications of treatment; requirement for further surgery**
Life impact	Physical/Social/Emotional/ Cognitive/Health Related Quality of Life	Pain; activity of daily living; quality of life; family life; psychological impact; school/pre-school attendance; sleep quality; sport participation**
Resource use	Economic/Hospital/Need for intervention/Social burden	NONE
Pathophysiological manifestations	Musculoskeletal	Hip mobility**
Death	N/A	N/A
Technical considerations	Technical/Surgical considerations	Acetabular coverage and hip congruency; evidence of arthritic changes; femoral head shape

** outcomes that were decided to be included following IPSG feedback.

5.3.6. DISCUSSION

The development of a COS was based on an in depth analysis of the literature, together with qualitative input from children affected by Perthes' disease, their parents and clinicians treating children with Perthes' disease. The COS consists of 14 outcomes that are important to both patients and clinical professionals. It is recommended that researchers ensure that they incorporate the COS when undertaking future high-quality clinical studies for Perthes' disease. It should be emphasised that this is a minimum dataset, and investigators remain free to add additional measures.

The relevance and use of COS has been already described across medicine (Boers et al., 2014; Singh, Dohm and Choong, 2017), propagated by the COMET-Initiative, who has gathered researchers with the common aim to develop COS for all conditions and treatments. Perthes' disease is an excellent example of why standardised outcome reporting is necessary, with the literature previously having 23 different outcome domains used to record "successful treatment" in Perthes' Disease. Nevertheless, despite the 23 different domains, there were domains of key importance to patients and families that had never previously been recorded, which only became evident from qualitative interviews. Furthermore, of the 23 domains in the literature, most studies would collect an assorted number of these domains without any consistency. Trying to synthesise useful information from these papers has therefore been difficult. The absence of clear outcomes is perhaps one of the main reasons for the wide diversity of treatments and opinions in the management of Perthes' disease – where treatment is based more on surgeon preference than scientific evidence (Hefti and Clarke, 2007). It is therefore unsurprising that the management of Perthes' disease is one of the key research priorities in children's orthopaedic surgery (Metcalfe et al., 2018).

The COMET-Initiative developed guidelines and standards to help maintain the quality of the COS development process (Boers et al., 2014; Singh, Dohm and Choong, 2017; COMET-Initiative, 2018). Across medicine there are a wide range of COSs for different conditions (e.g. paediatric asthma) (Sinha et al., 2012), however the orthopaedic community has perhaps neglected the importance of these (Ollivere, Marson and Haddad, 2019); with COSs available for only a few orthopaedic conditions (e.g. hip fractures) (Haywood et al., 2014).

The work in the current study has identified a list of core outcome domains to be measured and reported as a minimum in clinical research involving Perthes' disease patients. Whilst this COS defines which outcome domains should be measured, it does not provide detail on how the outcomes should be measured; indeed, this may vary depending on the patient population or in response to advances in measurement tools. Some outcomes (e.g. femoral head shape) may already be routinely assessed as part of clinical practice (Moghadam, Moradi and Omidi-Kashani, 2013), whereas other outcomes (e.g. sleep quality) are similarly important to families and require clinical and research teams to give consideration to how best to capture these outcomes. Likewise, outcomes such as hip mobility may be difficult to assess with an absence of objective instrumentations, so consideration also needs to be made as to how this can be achieved.

The current work was conducted using well-established guidelines and a robust methodology. The established methodology (COMET-Initiative and OMERACT guidelines) and the inclusion of perspectives from clinicians, patients and their families, are clear strengths of the study. The Delphi approach has been recommended as an ideal approach to identify outcomes of interest in clinical research (Sinha, Smyth and Williamson, 2011; Boers et al., 2014), yet ten different 'Delphi techniques' are

reported, and given this variation the rigour of the process has been questioned (Keeney, Hasson and McKenna, 2001). A major strength of the current work was to include qualitative interviews amongst affected children and families. It is acknowledged that the participants for qualitative interviews were from a single UK centre that may not necessarily represent the view of patients worldwide. However, patient, parent and clinician involvement in the Delphi was truly international, and only 5 new outcomes suggested at this stage had not already been identified. The discussion and feedback obtained at the IPSG involved 20 international surgeons and their opinions were sought to get important feedback into the development of the COS. It is acknowledged that the number of representatives attending the final consensus meeting was fewer than initially proposed in the protocol reported in chapter 3, yet the representation was broad in terms of the locations and distribution of members within stakeholder groups, and the interim discussion within the IPSG generated key points of discussion from a key interest-group to bring to the final consensus meeting.

In conclusion, the current study followed defined guidelines and methodology to develop a COS for clinical research in Perthes' disease. The adoption and acceptance of this COS in the paediatric orthopaedic community will help clarify the optimal treatment for Perthes' disease. Future work is required to clearly define the optimal outcome tools to record these outcomes, though it is hoped that this will be the catalyst to develop further clinical research amongst children with Perthes' disease.

CHAPTER 6

A LOW-COST WEARABLE DEVICE FOR MONITORING OF JOINT MOBILITY IN LABORATORY AND EVERYDAY ENVIRONMENTS

6.1. INTRODUCTION

There are many diseases of the musculoskeletal system, most of which affect mobility of the joints. The surgery for joint diseases and musculoskeletal disorders accounts for 25% of all surgery within the UK, at a cost of around £10bn per year (Arthritis Research UK, 2014). Beyond this, there are vast numbers of people with joint diseases not amendable by surgery owing to the nature of the illness (e.g. rheumatoid arthritis), or whose symptoms do not yet warrant surgery (Arthritis Research UK, 2014). The primary symptoms of joint diseases are activity-related pain (Dixon et al., 2007; Karachalios and Hartofilakidis, 2010) and a reduction in the normal range of motion of the joint (Bergström et al., 1985; Bekkering et al., 2001), which leads to difficulty in performing normal daily activities (e.g. walking). The management of these conditions is through lifestyle changes, medical treatments or surgery (Kim et al. 2006; Wang et al., 2015), with the aim of improving mobility and reducing pain (Roy and Crawford, 1988; Roddy et al., 2005).

It has been established, through the use of subjective quality of life questionnaires (Matcham et al., 2014), that joint stiffness reduces the ability to perform everyday activities (e.g. hip stiffness affects the ability to walk and can cause a limp), although there is no objective data measuring functional assessments of joint activity in day-to-day life. Indeed, existing methods to quantitatively assess joint mobility are suitable only for one-time measurements during clinical/laboratory assessment (e.g. manual goniometer; optical goniometer) (Mohamed, 2012; Zawawi, O'Keefe and Lewis, 2013). To measure the joint objectively for a prolonged amount of time, a dynamic measurement device is required, which is able to collect data in the natural environment of the patient (home; office; school). Such a device would be useful to monitor progression of disease or rehabilitation, and may be particularly useful in key

stages of the patient journey (e.g. post knee replacement), when remote monitoring may direct clinical teams to individuals in need of additional support (Jack et al., 2010).

Wearable technology is an emerging field in the health and clinical practice (Bonato, 2005), and devices which monitor real time data (e.g. heartbeat; body temperature) are already available (Zheng et al., 2014). Among these wearable devices, accelerometers have been largely used to assess activity level in adults and children population (Clark et al., 2016). However, the main role of accelerometers is to quantify the physical activity level rather than assess the joint mobility of the lower limbs. A part for accelerometers, devices that specifically aim to assess joint mobility use different sensors to obtain data from the joint of interest (Faisal et al., 2019). These sensors can be mainly summarised in 2 types (Faisal et al., 2019): i) optical (such as photodiodes); and ii) inertial (such as accelerometers and gyroscopes). Optical sensors convert light rays transmitted by an optical fiber (e.g. such in a fiber bragg grating – FBG - sensors) into an electrical signal (i.e. photodiode) or change their resistance when exposed to light rays (i.e. light dependent resistor – LDR). On the other hand, inertial sensors use acceleration (i.e. accelerometers) or orientation (i.e. gyroscopes) to detect movement of an object/person; and are usually both integrated in a single Inertial Measurement Unit (IMU) in order to obtain a more accurate reading of the data. Some of the current approaches in wearable devices for joint monitoring implemented FBG sensors, with good applicability in rehabilitation and orthopaedic settings (Pleros, Kanellos and Papaioannou, 2009) in detecting joint mobility and body posture (da Silva et al., 2011; Rocha et al., 2011; Abro et al., 2018). However, the design of these systems is bulky, restricted to the laboratory environment, and often includes expensive components. Additional devices to assess joint mobility through the use of optical sensors (e.g.

electro-goniometers) are suitable only for in clinic/laboratory measurements, with the additional factor of their expensiveness whit costs that can reach up to ~£1000 (Wang et al., 2011). Approaches implementing IMUs have obtained good reliability and validity of the data (Fong and Chan, 2010). However, the use of inertial sensors does have significant limitations in data processing (e.g. filtering; integration), which does require high hardware demands and thus higher costs and size for the processing unit, as well as difficulties in real time data processing (Fong and Chan, 2010), limiting their suitability for low-cost wearables. The idea to develop a low-cost electronic goniometer is not new (Wang et al., 2011), but to the best of the authors knowledge there are no low-cost solutions that are fully wearable outside the laboratory to assess joint mobility in everyday life. Therefore, the aim of this study was to implement a low-cost and practical solution to assess joint mobility, suitable for both short-term and long-term measurement of the joint angle in the laboratory and in the daily environments. This study outlines the development of a real-time, wireless and wearable system for the continuous monitoring of joint mobility in clinic settings aimed at patients with joint impairments or joint mobility issues, with the possibility to be implemented in everyday life.

6.2. DEVELOPMENT OF THE JOINT ANGLE MEASUREMENT DEVICE

A wireless monitoring device was developed, including a core microcontroller (ATMEL ATtiny85) with one optical flexible sensor, to detect changes in the joint motion (flexion/extension) (Figure 6.1).

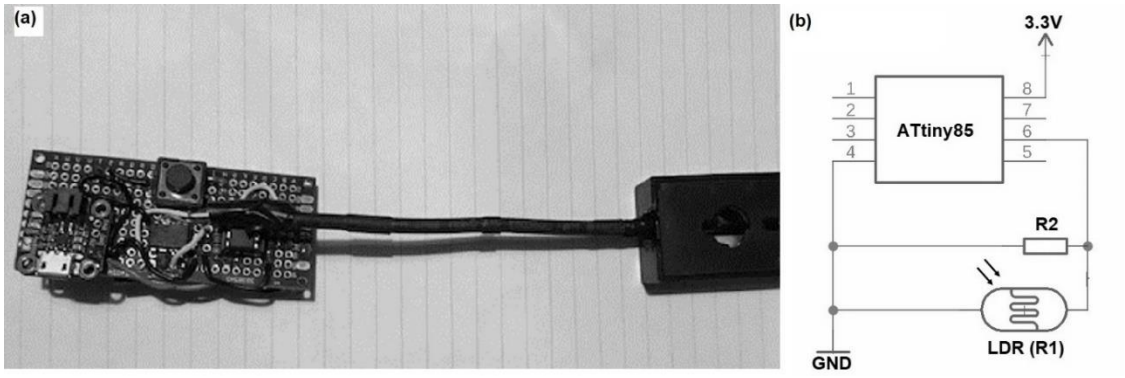

Figure 6.1. (a) Device prototype, showing the main board containing the microcontroller and the LDR (exposed); the POF; and the case containing the LED and the separated coin cell battery. (b) Schematic of the voltage divider circuit allowing the microcontroller to read changes in resistance from the optical sensor.

The device incorporates a Bluetooth interface (Tronixlabs HC-06) to send data for real time acquisition (laboratory setting) to a computer, and a local I2C EEPROM (Microchip 24LC256 IC) to allow for local data storage when the device is outside of the laboratory environment. The device runs at 3.3V and is supplied by a 3.7V 150 mAh lithium ion polymer battery, connected to a micro lipo w/microUSB jack charger to allow charging of the battery.

The optical flexible sensor is structured as a variable resistor inside a voltage divider circuit (figure 6.1b), containing a light-emitting diode (LED) to one side of a plastic optical fibre (POF), powered by an independent 3V 240mAh CR2032 coin battery and controlled by a switch to regulate the LED on/off status; and a LDR to the other side of the POF. The POF was isolated by external light interferences through an external coating made of black shrinking tubes. When the optical flexible sensor is bent (e.g. during flexion of a joint), the change in angle reflection of the light from the LED through the POF changes the amount of light received by the LDR, inducing changes

in its resistance. The bending of the optical flexible sensor induces macro-bending loss of the light that causes the change in the amount of light received by the LDR. These characteristics of a POF based sensor have been already described by Kim et al (Kim et al., 2014). The changes in light exposure to the LDR (R_1) increases its resistance, changing the output voltage (V_{out}) of the voltage divider connected to the micro-controller (with R_2 as a fixed resistor) which reads the different output voltage, following equation (6.1):

(6.1)

$$V_{out} = V_{in}\left(\frac{R2}{R1+R2}\right), \quad where, V_{in} = 5V$$

The value of R_2 as a middle value between the minimum and the maximum value reached by R_1 (in Ω) as set. Changes in R_1 are read by the microcontroller, which converts them to degrees and send the data to a PC/Laptop with a generic terminal client installed.

6.3. METHODS

The optical sensor was attached with simple tape to a manual goniometer while placing the goniometer in 5 different static angles (0º, 30º, 45º, 60º, and 90º), and recorded the first 10 seconds of measurement (acquiring data every 0.1 seconds) read by the device for each position. The average measurement for each angle and the Standard Error of Measurement (SEM) were then calculated.

The device was used to calculate changes in hip joint angle during some simulated daily activities (with a sample rate of 0.1 seconds) such as walking (on a treadmill at constant speed of 3Km/h) and sitting on a chair (performing a bodyweight half-squat test) (Figure 6.2a). Additional data were obtained placing the device on the knee (Figure 6.2b) and measuring changes in knee flexion/extension over time (sample rate of 0.1 seconds).

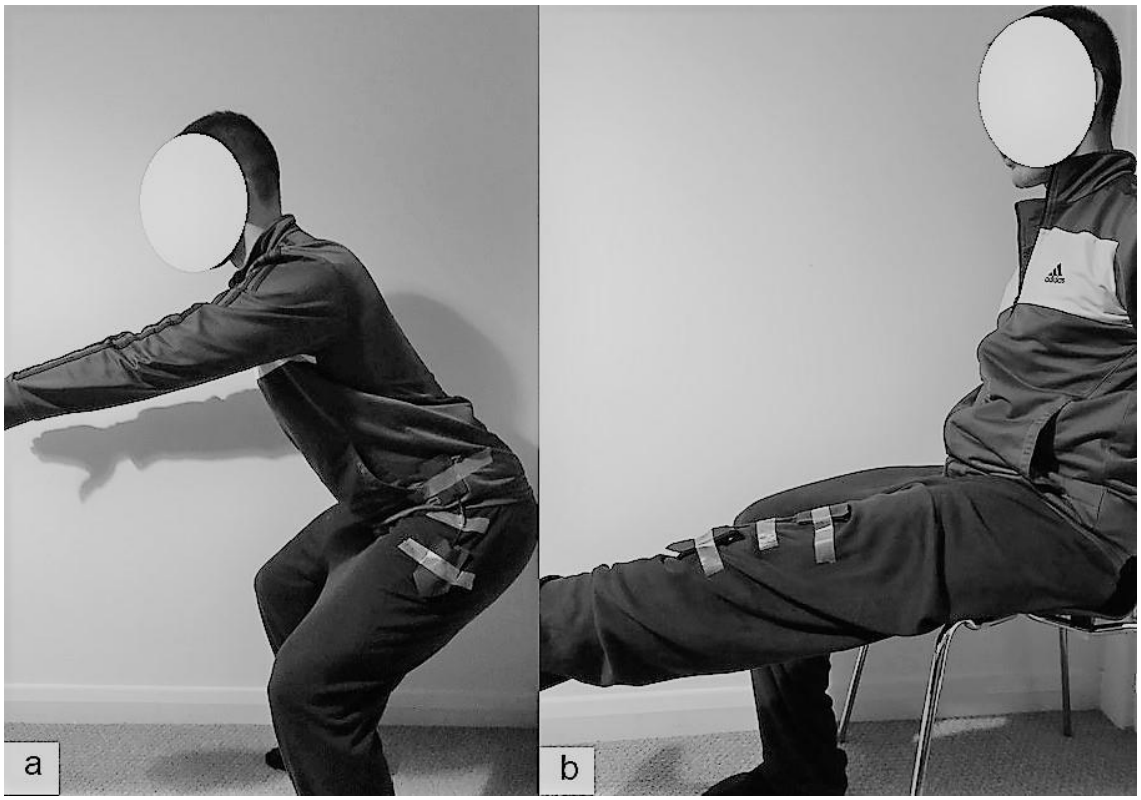

Figure 6.2. optical flexible sensor attached to the hip during a body squat (a) and to the knee during a knee flexion/extension (b).

6.4. RESULTS AND DISCUSSION

6.4.1. Device Response

Figure 3 shows the linear relationship between the changes in LDR resistance made by the POF bending, and the changes in bending angle detected by the device.

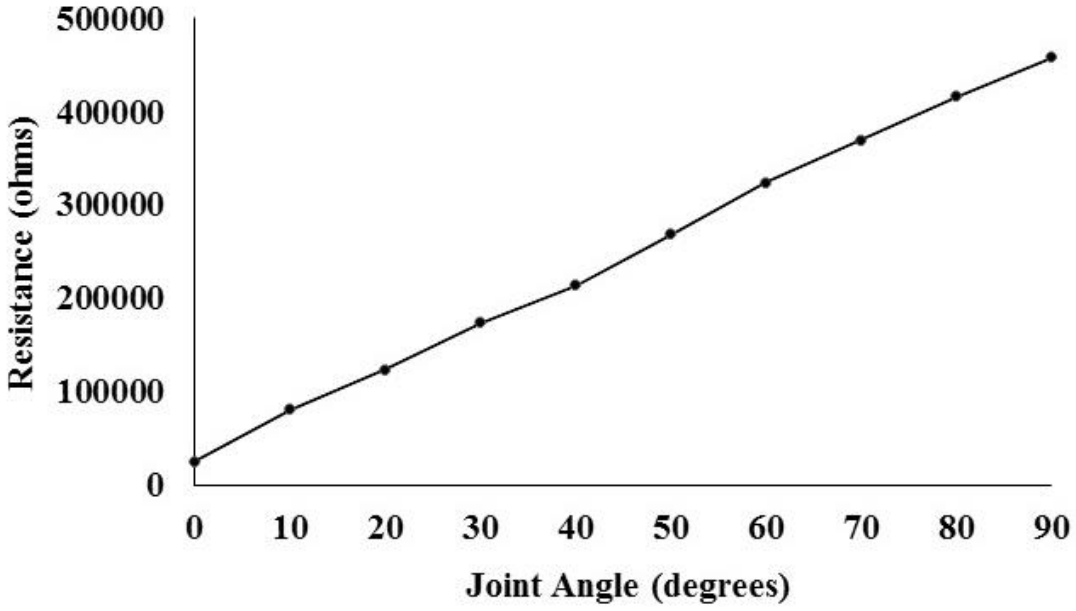

Figure 6.3. Linear relationship between changes in LDR resistance and device angle detection.

Table 6.1 shows the comparison between manual goniometer and the wearable device with SEM, at 95% Confidence Interval (CI). Figure 6.4 shows the comparison between the ideal angle measurement (goniometer) and the wearable device measurement.

Table 6.1. Comparison between manual goniometer and wearable device data.

Manual Goniometer Angle	**Wearable Device Angle Mean (±SEM*, 95% CI**)**
0º	1º (±0.27)
30°	31º (±0.27)
45º	44º (±0.27)
60°	61º (±0.27)
90º	89º (±0.27)

***Standard Error of Measurement*
***Confidence Interval*

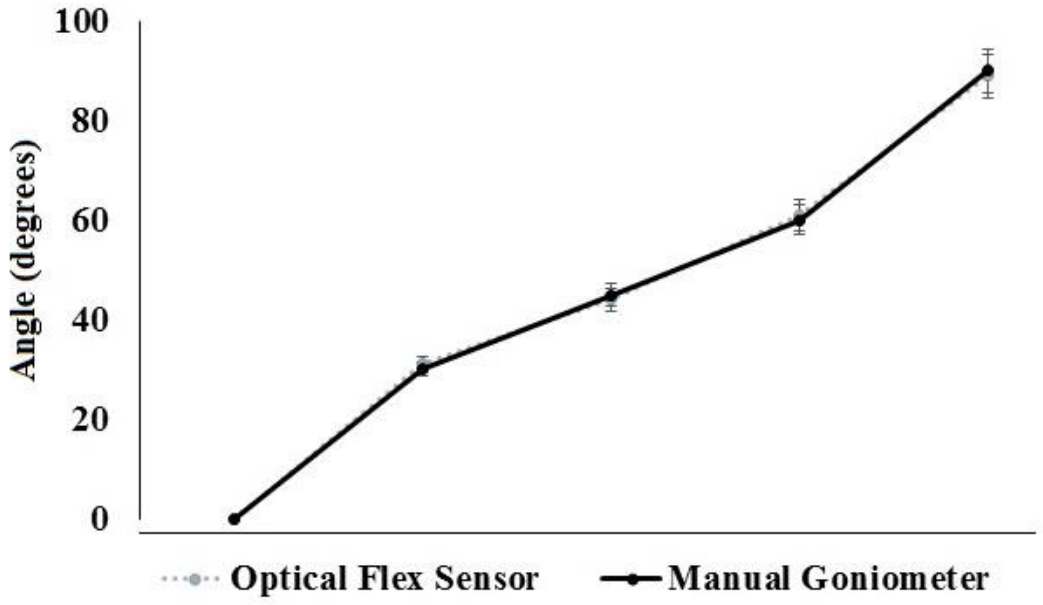

Figure 6.4. Comparison between manual goniometer (ideal angle measurement) and wearable device at 0°, 30°, 45°, 60° and 90°.

6.4.2. Data of example tests

Figure 6.5 shows the comparison between the data obtained by the device and the expected flexion/extension response of the hip while walking on a treadmill at a constant speed (3Km/h).

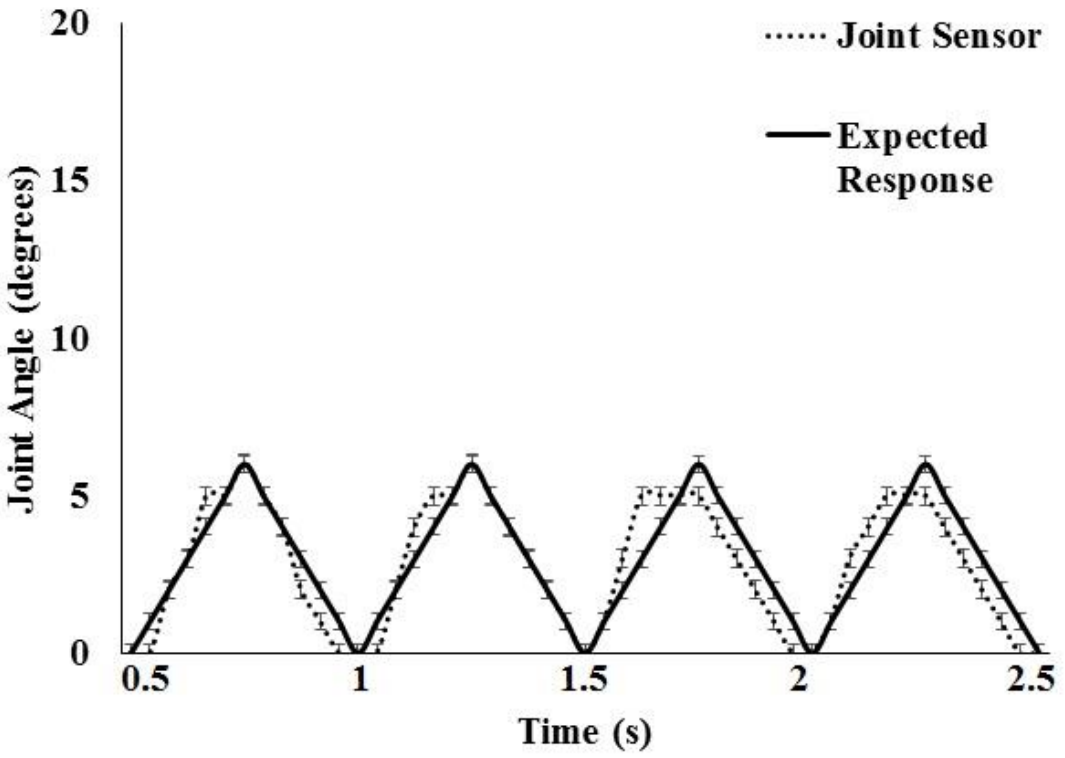

Figure 6.5. Change in hip joint angle during walking on a treadmill at constant speed (3Km/h).

Figure 6.6 shows the comparison between the data obtained by the device and the expected flexion response of the hip during body-weight half-squat test.

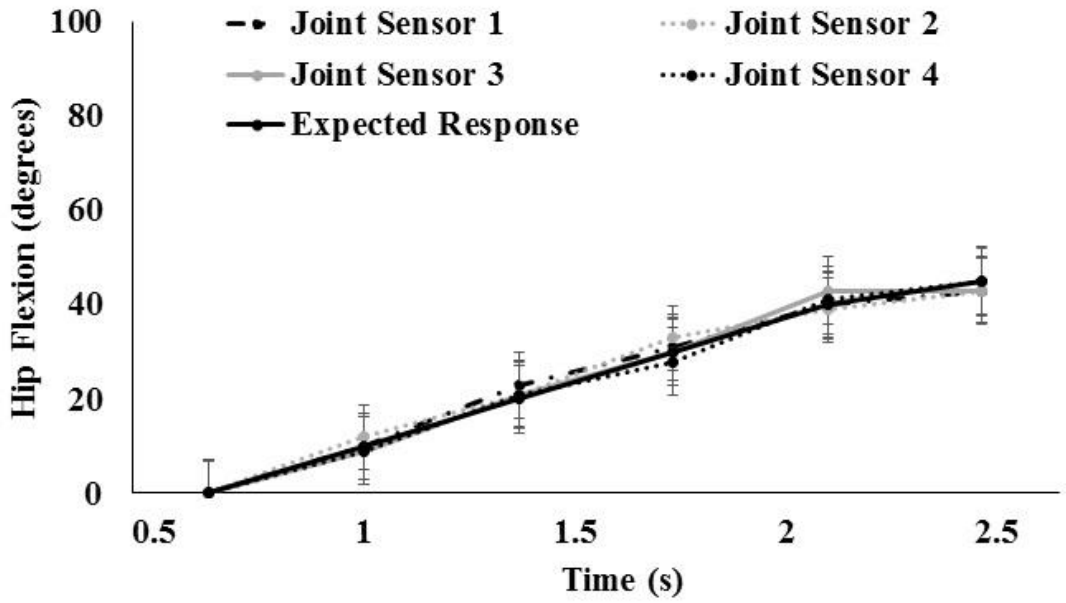

Figure 6.6. Change in hip joint angle during bodyweight half-squat test (hip flexion 45º).

To show the flexibility of use of the device, it was also examined the optical flexible sensor's ability in measuring changes in angle on other joints, such as the knee (Figure 6.7), and the elbow (figure 6.8).

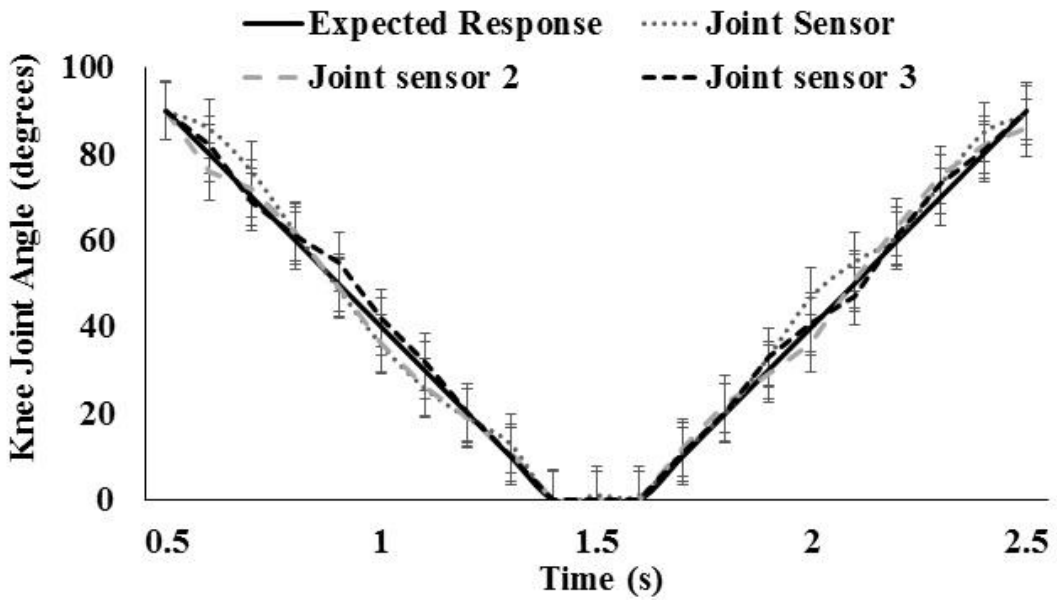

Figure 6.7. Changes in knee joint angle during flexion/extension in the seated position.

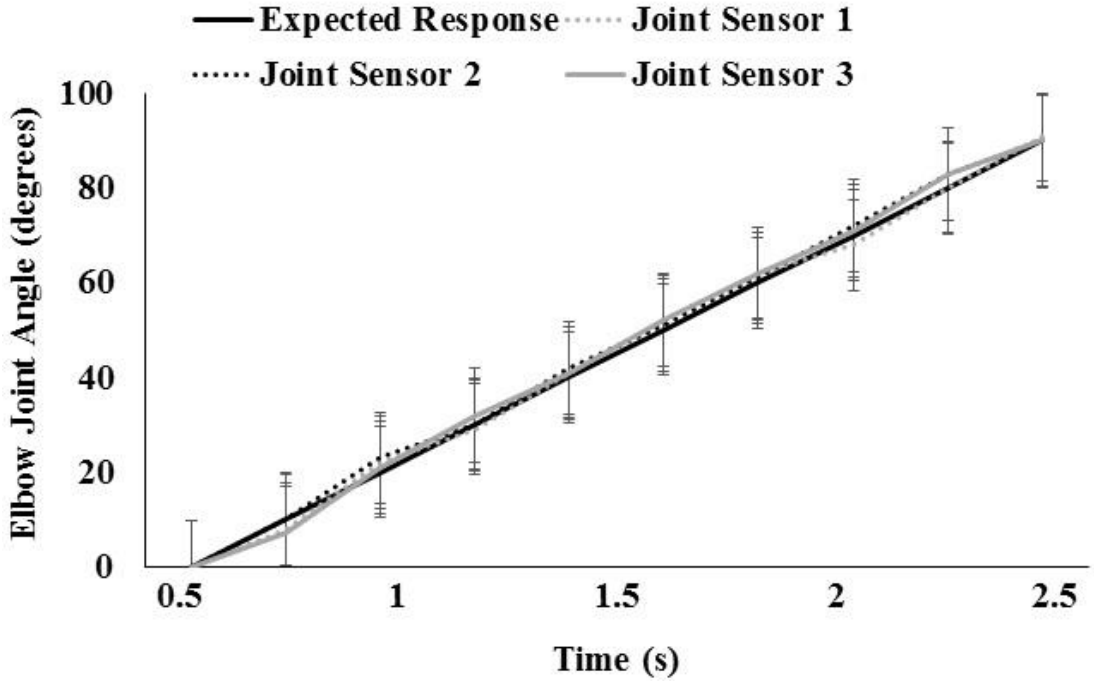

Figure 6.8. Changes in the elbow joint angle during flexion movement.

6.4.3. Cost Analysis

With the aim to keep the overall cost of the device as low as possible, low-cost components were used, easy to connect to any kind of PC/laptop with the only requirement to install any generic terminal client to allow communication with the device through Bluetooth 2.0. An approximate overall cost of the device components is given in Table 6.2.

Table 6.2. Cost of the individual components of the device at the time of publication.

Item	Unit Cost (£)*	Units	Total (£)
ATtiny85-20PU	3	1	3
BT Shield	3	1	3
LDR	0.5	1	0.5
LED	0.5	1	0.5
I2C EEPROM	0.5	1	0.5
Micro-lipo/MicroUSB Jack	5	1	£5
Lithium Ion Polibattery (3.7V, 150mAh)	9 (pack of 2)	1	£4.5
CR2032	0.5	1	0.5
POF	7 (100m)	10cm to 50cm	0.1
Grand Total			17.6

**Prices are indicative and may vary from seller to seller and by country*

Price shown in Table 6.2 do not include production material (e.g. soldering material)

The data demonstrate a consistent response in joint angle changes during each movement, indicating ability of the device in detecting joint angle. The data also show feasibility of the device in daily joint monitoring, as it is also able to recognize movements performed by the participant that replicate daily life activities. Moreover, the size ease of use and compact wearable design of the device allows inclusion of other body joints such as knees and elbows. Despite this, some limitations in the design of the device have to be taken in consideration. The sensor placement plays an important role on the correct reading of the joint angle by the device, thus any interference made by loose clothes need to be considered. The possibility to embed the sensor in a specific-made plaster or into clothes would reduce this variable. Additionally, the optic flexible sensor is detecting only movements on the hip frontal plane (flexion/extension), while the hip joint is a multiaxial joint. However, as reported by Charbonnier et al (2015), while hip flexion is highly required during movements of daily activities, adduction/abduction and internal/external rotation of the hip are quite limited. Thus, the use of a single axis sensor does not seem to have a possible impact on the validity of the collected data.

6.5. CONCLUSION

The aim of the study was to develop a low-cost wearable device to allow continuous monitoring of joint mobility in both laboratory assessment and everyday life to be used in patients with joint impairments or joint mobility issues. The device outlined in this study has shown good versatility in measuring joint range of motion when the individual is stationary and ambulatory, with a good accuracy of measurements compared to a manual goniometer (with a measurement error less than 1 degree). This

data provides preliminary evidence that a joint mobility device for laboratory use and everyday life monitoring is feasible. Moreover, the small design and flexibility of the device offers the potential to monitor all joints in the body. The developed system can be easily implemented and integrated into the clinical current joint monitoring procedures (such as manual goniometer; mobility tests) which are expensive, have limited effectiveness, are time-consuming and cumbersome. The attributes of the device outlined in this study will make it attractive to clinicians, physiotherapists, related professionals and researchers alike as it simplifies the monitoring procedure significantly and offers data collection when needed. Future work will investigate approaches of data analysis and learning algorithms to allow contextualization of the data in relation to joint mobility during specific body movements (e.g. sitting; walking). This will allow insight into the relationship between the specific movement and the degree of influence of the joint impairments. Further validation of the device will be conducted in a larger trial of monitoring joint stiffness in daily life activities of patients affected by joint diseases.

CHAPTER 7

HIP MOBILITY AND PHYSICAL ACTIVITY LEVEL IN CHILDREN'S HIP DISEASES

7.1. INTRODUCTION

Several conditions with varying clinical significance and severity can affect the hip joint in childhood, such as Perthes' disease (an idiopathic avascular necrosis of the developmental hip); hip dysplasia (DDH, where the acetabular roof does not fully cover the femoral head); and slipped capital femoral epiphysis (SCFE, where the femoral head slips off the neck of the femur) (Perry and Bruce, 2011; Zucker et al., 2013). Despite the cause (e.g. congenic or developmental), the main symptoms of childhood hip diseases are pain and limitations in hip joint mobility (Perry and Bruce, 2011; Zucker et al., 2013). These symptoms negatively influence the quality of life of these children, who usually have limitations in daily activities, such as walking down the stairs and performing physical activity (such as playing with their friends or doing physical education lessons in school) (Chapter 4).

Patient Reported Outcome Measures (PROMs), that assess the physical, emotional and social impact of a disease, provide information on the daily activities and the related quality of life (Miller, LeBovidge and Feldman, 2002; Palmen et al., 2014b). The National Institute of Health's Patient Reported Outcomes Measurement Information System (PROMIS) (Gershon et al., 2010) has been developed to help clinicians and researchers in collecting PROMs. The PROMIS questionnaires were designed to overcome some of the limitations present in other questionnaires to assess PROMs (such as difficulty in interpret scores; or difficulty in compare results among questionnaires) and standardise the tools used and the outcomes measured (Gershon et al., 2010). The PROMIS aims to detect differences in outcomes of diseases in adults and children, such as pain or limb limitations, and has already been used to assess the impact of different symptoms (e.g. pain; physical functions) on the quality of life of patients with paediatric conditions (e.g. Perthes' disease; Cerebral Palsy) (Kratz et al.,

2013; Matsumoto et al., 2019). There are different versions of the PROMIS, for example the PROMIS paediatric Mobility Short Form 8a (lower limbs), which specifically examines the impact of conditions on the mobility of the lower limbs, thus most relevant to children with hip diseases and currently employed as part of routine clinical practice in the UK.

A reduction in the mobility of the lower limbs, such as that observed in hip diseases, is likely to negatively affect the daily life of the children as well as their physical activity level. Physical activity is fundamental in the development of the musculoskeletal system and in the prevention of pathologies such as cardiovascular diseases, obesity and Type 2 diabetes (Pradinuk, Chanoine and Goldman, 2011; Boddy et al., 2014; Rush and Simmons, 2014). Nevertheless, the pain and the reduced mobility of the hip joint limit active participation in physical activities of children with hip diseases, supporting sedentary behaviour (e.g. sitting and lying), which may increase the risks for co-morbidities. There are a limited number of studies in the literature examining the impact of hip diseases on PA, and most employ only health-related quality of life questionnaires (e.g. EQ-5D-3L) (Novais et al., 2013; Hailer, Haag and Nilsson, 2014). Accelerometers have been effectively used in research studies to assess PA and sedentary behaviour in children (Strath, Pfeiffer and Whitt-Glover, 2012; Ramirez-Rico et al., 2014). However, no study has used accelerometers to assess if PA is reduced and sedentary behaviour is increased in children with hip diseases. Furthermore, no study has investigated if there is a correlation between mobility estimated using the PROMIS outcome tools, and the levels of PA and sedentary behaviour in children affected by hip diseases. The aim of the current study was to use accelerometers to objectively assess the physical activity levels of children

affected by hip diseases and correlate PA level to the PROMIS Mobility score (lower limbs) as an index of hip mobility.

7.2. METHODS

7.2.1. Participants: 28 children (12 boys and 16 girls – Table 7.1) aged 8 to 17 years old (mean 12±3 years; body mass 39±15 kg; height 147±17 cm) were recruited during routine clinical appointments for hip disease at Alder Hey Children's Hospital, Liverpool, UK. Patients were approached during the clinical visit by the research team; the study was explained verbally and in writing before informed consent was obtained. The study was ethically approved from the Research Ethics Committee and adhered to the 1964 declaration of Helsinki and its later amendments. Patient notes were screened by the clinician in charge to assess for study eligibility, which included children diagnosed with hip diseases (e.g. Perthes' disease; Slipped Capital Femoral Epiphysis, Developmental Hip Dysplasia - DDH) aged between 8 and 18 years old. Children with restricted activity that was not solely related to hip diseases (e.g. children with neuromuscular diseases); unable to adhere to the protocol (i.e. through learning difficulties or problems with communication); or with an enforced period of inactivity (i.e. bed rest period; wheelchair; cast) were excluded.

Table 7.1. Patients' characteristics.

Patient ID	Gender	Age	Condition	Surgery	Operated Hip
#001	Boy	9	Perthes' disease	Yes	Right

#002	Girl	8	DDH	Yes	Left
#003	Boy	10	Perthes' disease	Yes	Left
#004	Girl	15	SCFE	Yes	Both
#005	Boy	14	Perthes' disease	Yes	Left
#006	Girl	14	Perthes' disease	Yes	Right
#007	Boy	11	Perthes' disease	Yes	Left
#008	Girl	15	DDH	Yes	Right
#009	Girl	8	Perthes' disease	No	Right
#010	Boy	12	DDH	Yes	Right
#011	Girl	10	Perthes' disease	Yes	Right
#012	Girl	17	Avascular Necrosis of the Hip	Yes	Right
#013	Girl	11	DDH	Yes	Right
#014	Girl	14	DDH	Yes	Left
#015	Boy	15	Perthes' disease	Yes	Right
#016	Girl	12	DDH	Yes	Left
#017	Boy	8	Perthes' disease	Yes	Right
#018	Girl	12	SCFE	Yes	Right
#019	Girl	14	DDH	Yes	Right
#020	Girl	11	DDH	Yes	Right
#021	Girl	8	Perthes' disease	Yes	Right
#022	Girl	11	Perthes’ disease	No	N/A
#023	Girl	10	Perthes' disease	Yes	Left
#024	Boy	10	Perthes' disease	Yes	Right
#025	Boy	9	Perthes' disease	No	N/A
#026	Boy	14	Perthes' disease	No	N/A
#027	Boy	15	SCFE	Yes	Both
#028	Boy	13	Perthes' disease	Yes	Right

DDH=Development Dysplasia of the Hip; SCFE Slipped Femoral Capital Epiphysis

7.2.2. Experimental design: Following informed consent, children completed the PROMIS paediatric item bank v. 2.0 –Mobility Short Form 8a (lower limbs), which is used clinically for evaluate impairments in lower limbs mobility; and wore a hip based accelerometer (ActiGraph) for objective assessment of physical activity for 7 days.

7.2.3. Measurements:

a) PROMIS Questionnaire. Participants completed the PROMIS paediatric item bank v. 2.0 –Mobility Short Form 8a (lower limbs) (Gershon et al., 2010; HealthMeasures, 2019a). The questionnaire has 8 items whose investigate the general impact that patient's lower limbs mobility has on his or her daily activity tasks (such as playing with friends; or walk up the stairs), and whose can be scored from 1 (*not able to do it*) to 5 (*with no trouble*). As per PROMIS guidelines (HealthMeasures, 2019b), raw score was calculated as the sum of each item score. Scale score was calculated from raw score using the PROMIS conversion table (HealthMeasures, 2019b).

b) Physical Activity. Physical activity was monitored using a tri-axial accelerometer (Actigraph wGT3x-BT). Participants wore the accelerometer on their right hip for 7 consecutive days, removing the device for sleeping and water-based activities (as the monitors are not waterproof); and recorded the times the device was worn and took off each day on a diary sheet provided. Accelerometer non-wear time was defined as 90 consecutive minutes of zero counts.min^{-1} (Choi et al., 2011). Inclusion criteria for analysis were ≥7 hours of wear time per day (Corder et al., 2008), for a minimum of 4 days, including one weekend day (Trost, Mciver and Pate, 2005). The ActiLife software, version 6.2 (ActiGraph, Pensacola, Florida) was used to download the data to a computer, and to perform scoring and wear-time validation analysis. Raw acceleration data was converted to 60s-epoch activity count data (counts·min^{-1}). PA

intensity was determined using the following cut points (Freedson, Pober and Janz, 2005): light (≥150 counts.min-1), moderate (≥500 counts.min-1), and vigorous (≥4000 counts.min-1). PA data were exported and handled in Excel (Microsoft), and total time (minutes) spent in light, moderate and vigorous PA was calculated (Figure 7.1).

7.2.4. Statistical Analysis

Data was checked for outliners, and Shapiro-Wilk Test was employed to ensure residuals were normally distributed ($p>0.05$). A Bivariate Pearson Correlation Test (two-tailed) was employed to examine linear correlations between the average daily PA in minutes (sedentary time - ST; light – LPA; moderate-vigorous – MVPA; vigorous – VPA) and PROMIS questionnaire Scale Score. A one-way ANCOVA was employed to examine differences in PA levels (ST; LPA; MVPA; VPA) among groups divided by PROMIS Scale Score (moderate; mild; normal). Analysis were adjusted for the effects of age, BMI, height, weight and accelerometer wear time. Statistically significant group differences were followed up with Bonferroni pairwise comparisons. The statistical analysis was performed using SPSS software v26.0 (IBM).

7.3. RESULTS

7.3.1. Activity Monitors. Average daily ST was higher (73% of wear time) than average daily Total Activity (TA) time (27% of wear time). Of the average daily TA, the highest amount of time was spent in MVPA (18%), with remaining activity time spent in LPA (8%), and only 1% of the activity time spent in VPA (Figure 7.1).

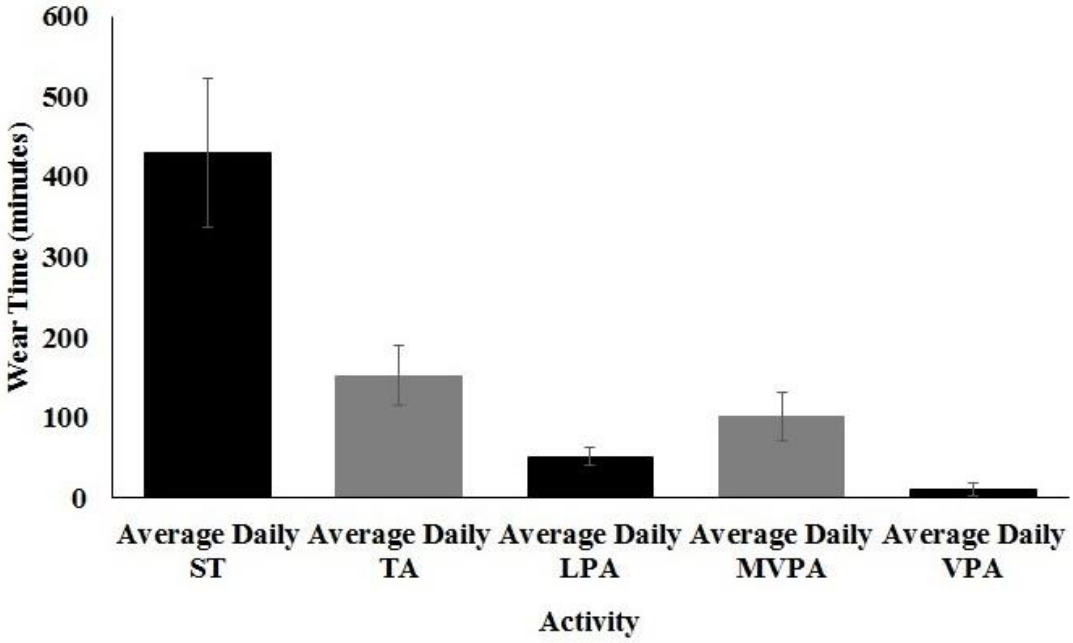

Figure 7.1. Children's PA data collected using accelerometers. ST=Sedentary Time; TA=Total Activity; LPA=Light Physical Activity; MVPA=Moderate-to-Vigorous Physical Activity; VPA=Vigorous Physical Activity.

7.3.2. PROMIS Questionnaire. The overall score of each PROMIS questionnaire was converted in the Scale Score and the results were classified in Severe, Moderate, Mild and Normal functions, based on the PROMIS cut scores on physical function metric (Figure 7.2) (Cella et al., 2010) to establish the degree of limitation in the lower limbs. 30% of the children reported "normal function" (Scale Score ≥50); 44% reported "mild limitations" (Scale Score 40 to 48); and 26% reported "moderate limitations" (Scale Score 30 to 40) (Figure 7.3).

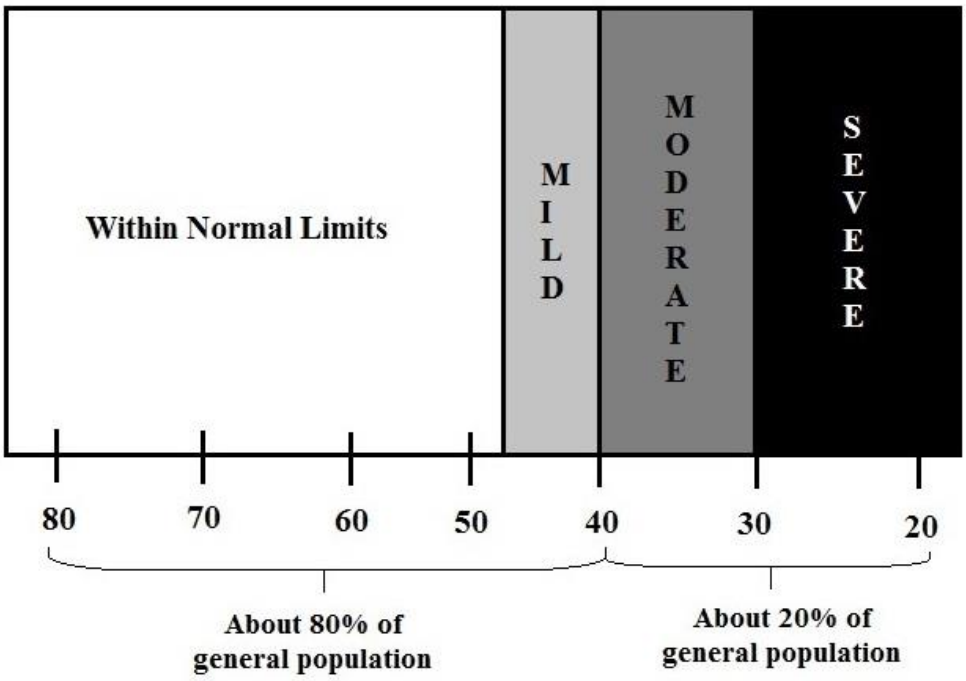

Figure 7.2. PROMIS cut scores on physical function metric (Cella et al., 2010).

Table 7.2. PROMIS raw score and the Scale Score for each child.

Patient ID	Raw Score	Scale Score
#001	37	46
#002	40	59
#003	34	41
#004	22	30
#005	30	37
#006	36	45
#007	37	46
#008	32	39
#009	31	38
#010	33	40

#011	37	46
#012	24	32
#013	40	59
#014	33	40
#015	40	59
#016	38	48
#017	39	52
#018	40	59
#019	34	41
#020	31	38
#021	27	34
#022	40	59
#023	22	30
#024	40	59
#025	39	52
#026	39	52
#027	38	48
#028	40	59

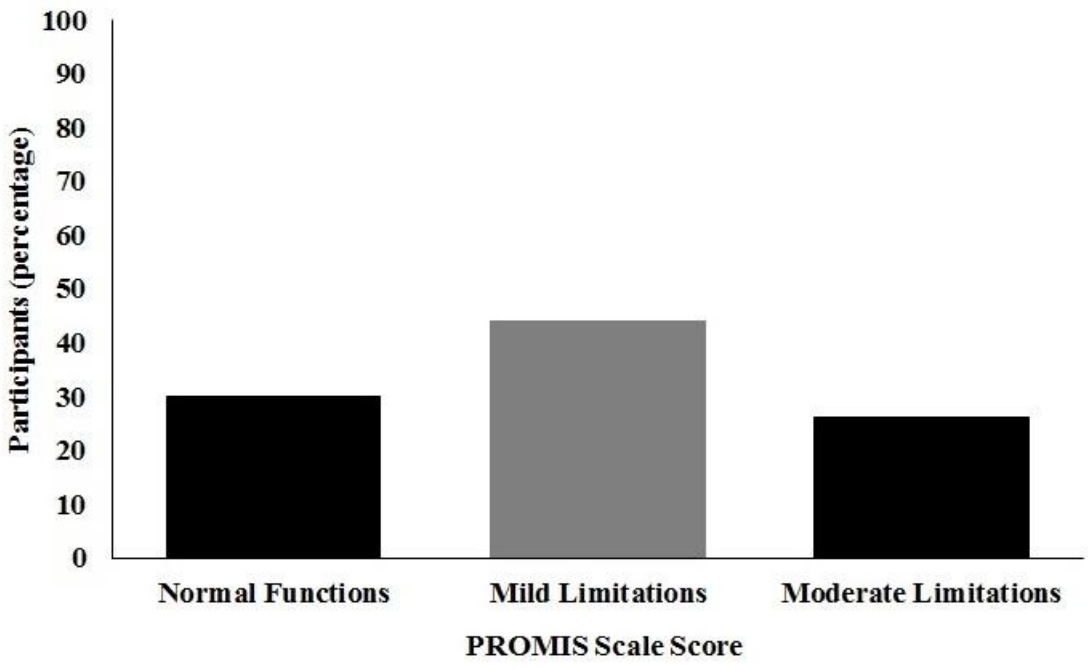

Figure 7.3. PROMIS scale score results.

7.3.3. Correlation between PA and PROMIS Scale Score. There was evidence of a moderate to strong correlation between the average daily MVPA and the overall Scale Score of the PROMIS questionnaire *(**r**=0.67, **n**=28, **p**=0.01)* (Figure 7.4a). A moderate correlation was evident between the average daily LPA and the overall Scale Score (***r**=0.46, **n**=28, **p**=0.01*) (Figure 7.4a). A moderate correlation was evident between the average daily VPA and the overall Scale Score (***r**=0.54, **n**=28, **p**=0.01*) (Figure 7.4a). No correlation was detected between the average daily ST and the overall Scale Score (***r**= -0.28, **n**=28, **p**=0.15*) (Figure 7.4b).

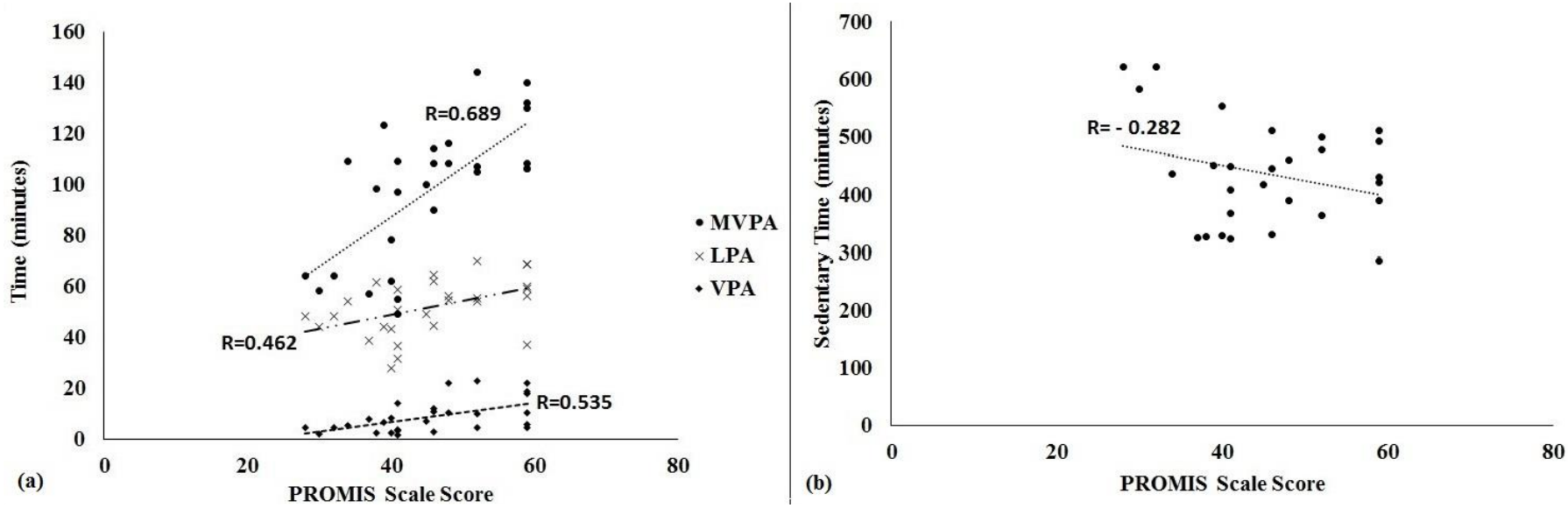

Figure 7.4. (a) Correlation between PA time and Scale Score. (b) Correlation between ST and Scale Score. LPA=Light Physical Activity; MVPA=Moderate-to-Vigorous Physical Activity; VPA=Vigorous Physical Activity.

7.3.4. Differences in PA level among PROMIS Scale Score Groups. There was a significant difference in Sedentary Time (p=0.002); MVPA (p=0.002) and VPA (p=0.004) among Scale Score sub-groups. ST was lower in the normal group compared to the moderate (54.3±13.8 minutes, p=0.00) and the mild (36.6±12.3 minutes, p=0.02) groups; but not statistically significant difference in ST was found between the moderate and the mild group (17.6±13.0 minutes, p=0.58). MVPA was higher in the normal function group compared to the mild (33.4±10.6 minutes, p=0.01) and moderate (48.6±12.0 minutes, p=0.00) groups; but not statistically significant difference in MVPA was found between the mild and the moderate group (15.2±11.3 minutes, p=0.57). Additionally, VPA was higher in the normal function group compared to the moderate group (11.0±2.9 minutes, p=0.00), but not statistically higher than the mild group (6.5±2.6 minutes, p=0.64). There was no difference in LPA between groups (p>0.05).

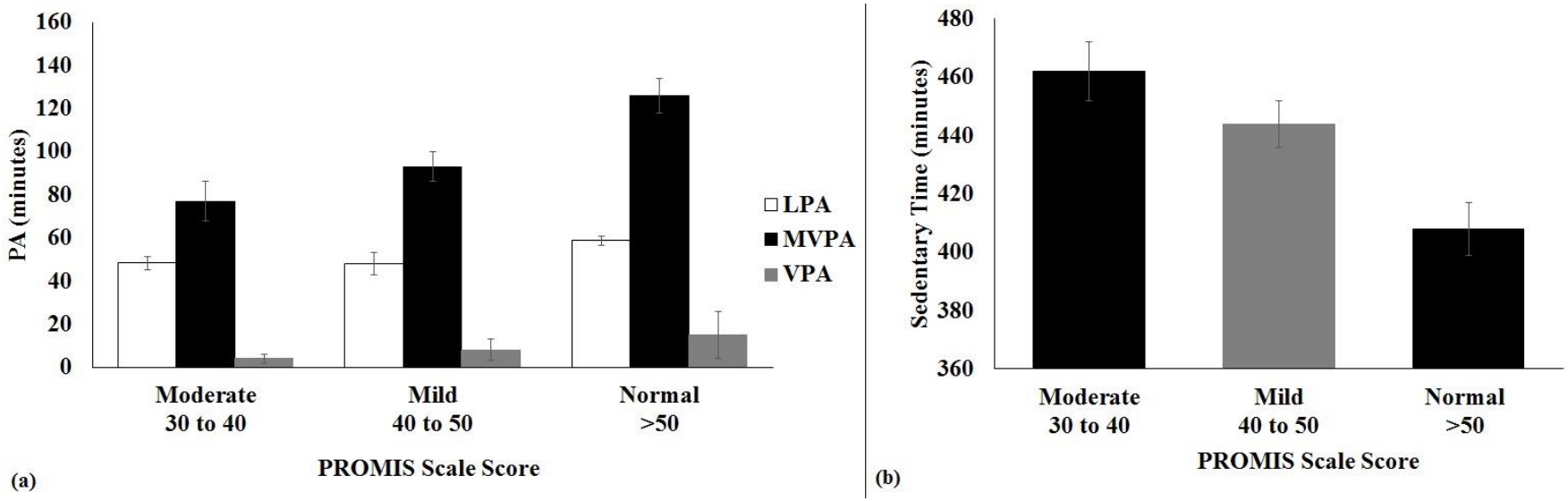

Figure 7.5. (a) Children's average daily MVPA divided by PROMIS Scale Score. (b) Children's average daily ST divided by PROMIS Scale Score. PA=Physical Activity; LPA =Light Physical Activity; MVPA=Moderate-to-Vigorous Physical Activity; VPA=Vigorous Physical Activity.

7.4. DISCUSSION

The aim of the current study was to objectively assess the PA level in children with hip diseases and correlate PA with the PROMIS lower limbs mobility score to understand if limitations in mobility assessed using the current tool used in clinical practice impacted on the amount of PA performed in these children. Intriguingly, the PA level of these children was higher than the average daily MVPA recommended by guidelines. LPA, MVPA and VPA were positively correlated to PROMIS Scale Score, where children with normal mobility having higher PA levels and lower sedentary time.

This is the first study to investigate the correlation between mobility and PA level of children affected by hip diseases. The results suggest that a lower PROMIS scale score (which indicates impairments in the lower limbs mobility) corresponded to a lower level of daily moderate and vigorous PA that children with hip diseases perform. ST; average daily MVPA; and VPA were all affected by the mobility score, where children with the lower functions being the less active and children with normal functions being the most active. This study provides experimental data to provide external validity and supporting evidence that the PROMIS Mobility Score can provide a general overview on the PA level of these children.

The PROMIS, from the current study population, suggests 70% of children have some type of physical limitation and 30% report normal function. Understanding the limitations induced by hip diseases is important as they have negative impact on the general quality of life of these children (Chapter 4; Hailer, Haag and Nilsson, 2014), but whether this translates into reducing their ability to perform daily physical activity such as walking was unknown. Accelerometers were employed in the current study to

measure PA levels in children with hip diseases. Intriguingly, the results show that the average daily MVPA of these children is of 101±37 minutes. The daily MVPA recommendation for children is at least of 60 minutes per day (Oja and Titze, 2011) and the data suggest that children with hip diseases are exceeding the recommended PA levels. Previous observational studies, employing accelerometers to measure PA in healthy children in England (Scholes and Mindell, 2016) and in Liverpool (Ramirez-Rico et al., 2014) suggest recommended daily MVPA is reached in 22% of the English children and in 27% of the Liverpool children. Therefore, the children affected by hip diseases in this study seem to be more active than the general population, having an average daily MVPA 68% higher than the minimum suggested by the guidelines. The objective PA data in the current study also support the only previous study to investigate the impact of hip diseases on PA. The study conducted in patients with Perthes' disease in Sweden employed physical activity questionnaires (EQ-5D-3L and IPAQ) (Hailer, Haag and Nilsson, 2014) and observed higher PA level in Perthes' disease population compared to the national average. The authors linked the higher PA levels in that study to hyperactivity related to attention deficit hyperactivity disorder (ADHD), a possible cause of Perthes' disease (Hailer, Haag and Nilsson, 2014; Hailer and Nilsson, 2014). However, the data of the current study included 40% of children with other types of hip disease other than Perthes' disease, showing that higher level of PA seems to be common to children with hip diseases. Indeed, while hyperactivity may be true in some cases, it is more plausible that the high level of PA reported by the children participating in the current study is related to the importance given by their parents on PA to help ease pain or as a method to increase the general wellbeing of their children. Alternatively, these children may perform more general PA due to limitations on other activities such as sport or impact

activities. It is also important to note that different hospitals have different guidelines and approaches to the PA and exercise level that children with hip diseases should perform. Indeed, while some hospitals put strict limitations to the amount of PA that these children can have during the day (suggesting approaches that involves wheelchairs or bed-rest, and supporting a sedentary lifestyle), some other centres have more flexible guidelines. Alder Hey Hospital, where the current study population were recruited from, for example, supports an active lifestyle for children with hip diseases, limiting only activities that have high impact on the hip joint (such as jumping on trampolines). This may have influenced the results of this study of which recruited children were more supported to undergoing PA compared to children affected by hip diseases managed in other centres. It is also important to note as possible bias that children recruited in the study may have modified their behaviour in response to wearing the device, being more active than usual; or that only children who were the most active took part in this study. Thus, further investigation on the PA level of these children is required to support these findings and understand better the PA patterns of this population. A final consideration has to be done on the choice of the accelerometers' intensity related cut-points. Different authors have proposed different cut-points that vary between population (e.g. adults and children), age-range, and accelerometer's type (e.g. ActiGraph), with some of them that may incur in overestimating or underestimating of the PA level (Trost et al., 2011). This may induce inconsistences in data result among studies, and thus difficulty in comparing them. Debates are still ongoing on the best cut-points to adopt for accelerometers studies, however the cut-points defined by Freedson et al (2005) for ActiGraph accelerometers and employed in this study have shown significantly better classification accuracy for MVPA compared to cut-points defined by other authors (Trost et al., 2011).

Sedentary time in children participating in this study was higher than the ST reported among healthy English children (Craig, Mindell and Hirani, 2009). Children with moderate limitations reported a ST of 1.8 times higher than the average, while children with mild to normal functions reported a ST 1.6 times higher than the average. This may be due to the limitations induced by the hip condition (such as pain in the hip joint) which may increase the time these children spend sitting or lying down in the bed, especially during the bad days where the symptoms are worse (Chapter 4). Increased sedentary time in children has been observed to be a risk factor for cardio-metabolic risk, obesity and other co-morbidities (Biddle et al., 2010; Boddy et al., 2014). Sedentary-induced risk factors, such as obesity, may also play an additional role in the worsening of the symptoms and manifestation of the hip condition (Neal et al., 2016; Perry et al., 2018; Shore et al., 2018), and negatively influence the clinical management of these children (Novais et al., 2015). Therefore, based on the findings of the current study, interventions targeting breaking up sedentary time in children with hip diseases are warranted.

This study adds important data on the PA level of children with hip diseases, and the influences that lower limbs mobility has on PA and sedentary behaviour. Strengths of the study were the use of both qualitative and quantitative data to obtain an in-depth picture on the PA level of these children. Additionally, the use of validated measurements such as the PROMIS paediatric lower limbs mobility questionnaire and the accelerometers add reliability to the results. Nevertheless, it is acknowledged that the data was collected in a single UK centre, which does limit the range of the patients and may have influenced the population of children recruited. A multi and international centre study would provide a broader range of hip diseases and clinical management approaches.

In conclusion, this study suggests that the PROMIS lower limbs mobility tool is correlated to the PA level of children with hip diseases and provides a general overview of PA. Children reporting a higher mobility perform more PA than children with lower mobility. Whilst, the general mobility of these children is low with most reporting moderate to severe limitations, daily PA levels are generally higher than daily minimum MVPA recommended for children. However, ST is higher in children with hip diseases compared to a healthy population.

CHAPTER 8

GENERAL DISCUSSION

8.1. Major Findings

The novel work undertaken in this thesis has generated new knowledge for the literature and for clinical practice. The main findings of this thesis are:

(i) A Perthes' disease specific COS has been defined to be employed in future clinical trials;

(ii) A prototype of a low cost wireless monitor has been defined to assess hip mobility, a core outcome in Perthes' disease;

(iii) The current subjective clinical tool to assess hip mobility in childhood hip diseases is strongly correlated with objectively measured physical activity.

8.2. General Discussion of Main Findings

8.2.1. Core Outcomes Set for Clinical Trials in Perthes' Disease

Core outcomes sets for clinical trials are important as they contribute to the definition of clear guidelines for the management of clinical conditions. A key theme in the current thesis, outlined in chapters 3-5, was the synthesis of the literature, which indicated the current outcomes measurements were inconsistent and wide ranging. This suite of studies together with key stakeholders' input has enabled the generation of a COS for Perthes' disease that included 14 physical, emotional and social outcomes. This minimum set of core outcomes for Perthes' disease will help researchers and clinicians to measure key and consistent outcomes that are relevant to surgeons, patients and parents in future studies. Additionally, the COSs in Perthes' disease research is relevant to both patients' associations (e.g. Perthes Association UK) and funding bodies (e.g. NHIR) to clearly identify research value and better guide priorities in research.

The COS is clearly defined in this thesis but there are some noteworthy considerations and limitations to its current state:

1. *Number of participants included in the Delphi survey*: There was a high drop-out rate of the participants in round 2 of the survey. This is common in Delphi surveys, usually due to the length of the questionnaires and the amount of time it takes for participants to complete the survey. Nevertheless, a high drop-out rate is unlikely to induce any systematic bias to the study (Mullen, 2003) and thus it did not impact the validity of the results.
2. *The large number of outcomes included in the final COS*: the defined COS has summarised 14 outcomes, which is a high number of outcomes to collect data on in any given study. Other well established COSs, such as for rheumatoid arthritis (Felson et al., 1993), include no more than 7 outcomes. Nevertheless, most of the outcomes that have been included in the defined COS for Perthes' disease (e.g. pain; quality of life; activity of daily living) can be easily collected by a few patient-reported measurements tools (such as the Harris Hip Score which includes items for pain, quality of life, and activity of daily living), reducing difficulties in data collection. Conversely, the COS does not limit researchers and clinicians to only collect these 14 outcomes: other outcomes can be additionally measured in individual studies.
3. *How to measure the COS*: The COS for Perthes' disease simply states the outcomes to be measured with no information on how to measure them. As outlined above some outcomes, such as quality of life, activity of daily living and pain can be measured with the use of PROMs such as the HHS. However, for some outcomes, there are currently a number of tools to assess the same

outcomes (e.g. hip pain can be assessed with different scales, such as the HHS or the WOMAC) inducing confusion on the best tool to choose. Content validity assesses the degree at which the content of a measurement tool reflects the construct to be measured (Prinsen et al., 2016). All items from a PROM should be relevant to the construct and also understood by patients. The COSMIN (COnsensus-based Standards for the selection of health Measurement INstruments) Initiative (Prinsen et al., 2016) aims to define the most appropriate measure for each outcome, helping the practical application of COSs and their consolidation in research as well as in clinical practice. Additional work, following the guidelines reported by COSMIN, are now required to validate a set of standard measurements to support the COS for Perthes' disease.

4. *The inclusion of sport participation as a core outcome*: The findings of this thesis suggest that sport participation and physical activity are important outcomes to children with Perthes' disease. These children are often excluded from sport activities and have a reduced activity level due to the limitations induced by the disease (Chapter 4). To date only one study has investigated the PA level in children with Perthes' disease (Hailer, Haag and Nilsson, 2014). The lack of studies that have investigated PA level in children with Perthes' disease may be due to the lack of interest from surgeons on this outcome, which until reported from the studies in this thesis (chapter 4 and 5) has not been considered important in clinical management. Moreover, PA level of these children is often difficult to assess with current clinical tools that often rely on subjective measurements, such as health and physical activity related questionnaires (e.g. EQ-5D-3L). Accelerometers as an objective measurement

of PA have been largely used in studies to assess the PA level of healthy children, but no study has used them to assess the PA level in children with Perthes' disease and more in general with hip diseases, nor are accelerometers employed in clinical practice. Thus, in chapter 7 accelerometers were used to assess the PA level in children with hip diseases. Children with hip diseases demonstrate higher MVPA that the minimum of the daily 60 minutes recommended by guidelines, but these children have a high level of sedentary time. These findings support the difficulties reported by the children (especially during the bad days, were the symptoms of the disease are worse) in reducing the amount of time spent laying on the bed or on the sofa due to the limitations induced by the disease (Chapter 4). Whilst, the inclusion of sport participation and PA as a core outcome in Perthes' disease might seem surprising, the findings from this thesis (Chapters 4, 5, 7) clearly provide evidence that this outcome is important.

5. *How to measure sport participation and PA in Perthes' disease*: Various studies, including the studies within this thesis, have shown that the quality of life of children with hip diseases is affected by the symptoms of the disease such as pain and reduced mobility of the hip joint (Miller, LeBovidge and Feldman, 2002; Hailer, Haag and Nilsson, 2014). These limitations impact the ability of the children to walk, and promote behaviours such as sitting and lying for long periods. The findings of this thesis suggest that enabling walking without pain and reducing sedentary behaviour in children with Perthes' disease are priorities in the prevention of more serious diseases in adulthood. Currently, the only clinical tool to assess the mobility of these children (e.g. the amount they can walk without limitation) is via the PROMIS questionnaire

for paediatric lower limbs mobility. This assesses the degree of limitation in lower limb mobility that these children have due to their disease and is used as a surrogate marker of physical activity. In chapter 7, the PROMIS mobility score of children with hip diseases was assessed and correlated with objectively measured PA and sedentary behaviour. PROMIS mobility score was positively correlated with LPA, MVPA and VPA but not with sedentary behaviour. These data support the use of PROMIS as an indirect tool to assess the general activity level of these children, despite it does not provide a useful marker of sedentary behaviour. Therefore, PROMIS can be used as a tool to measure mobility and PA as part of studies assessing COS in Perthes' disease.

8.2.2. Development of a Low-Cost Sensor to Monitor Joint Mobility in Everyday Life

Chapter 5 outlined that hip mobility was an important outcome of relevance in Perthes' disease for surgeons, patients and parents. Impairments in hip mobility affect the quality of life of children with hip diseases (Chapter 4) that influences their physical activity level (Chapter 7). Despite several methods to assess hip mobility in clinical practice (including the PROMIS questionnaire), there is none that can assess hip mobility for a prolonged period of time in the everyday life environment of the patients.

The identification of the main outcomes to develop a COS is the first step to improve data collection and reporting in clinical trials; but often these outcomes cannot be successfully assessed with the instrumentation available. For example, hip mobility, a key outcome for Perthes' disease (and more in general for hip diseases) has no

adequate *objective* tool to be used in clinical practice. This is because the current instrumentation is confined to laboratory/clinic use only and cannot collect data during the daily tasks that patients perform every day. In an attempt to overcome these limitations, in chapter 6, a low cost wearable hip sensor was described to collect data on joint mobility for patients with joint impairment, which could be employed to monitor hip mobility in children with hip diseases in their daily environment. The preliminary tests demonstrated that the prototype has good accuracy (compared to a manual goniometer when assessing joint angle in static position). The ability of the sensor to remotely collect data outside the laboratory environment makes the device useful to improve the understanding of the influences that hip stiffness has on daily tasks. Additionally, its low manufacturing costs make it convenient for both hospitals and small clinics, without the need to spent huge amount of money in more expensive tools.

The sensor described in this thesis has the ability to measure the hip range of motion during everyday tasks. Nevertheless, there are some noteworthy interrelated modifications that are required:

1. *Wearability:* The original aim was to collect hip mobility data using the device described in chapter 6 on hip mobility of the recruited children with hip disease in chapter 7. Nevertheless, the following issues were encountered during the data collection process. Attachment of the device to the clothes with tape only worked when the clothes were tight fitting. Loose clothing including school skirts for girls prevented adequate data collection. Incorporation of the device into clothing (e.g. shorts) or a dressing (e.g. surgical plaster) are required to ensure necessary contact with the hip.

2. *Device size:* Miniaturisation of the device is required to allow it to easily fit inside clothes or a dressing to allow the sensor to be wearable for prolonged period of time and outside the laboratory setting.
3. *Power consumption:* The power supply plays and important role in the successful implementation of a wearable device. To allow data collecting for long periods (e.g. a week), the power consumption of the device needs to be low and the battery choice has to be adequate to supply enough power to avoid voltage drops during this period. Currently, the device is powered by a 3.7V lithium battery with a 150mah capacity, which is enough to keep it powered up for at least 24h while keeping the design small. However, additional work on the circuit board design and on the microcontroller's efficiency needs to be performed in order to further reduce the power consumption of the device and allow to increase its recording time without affecting its wearability.
4. *Data interpretation:* The data collected in chapter 6 was obtained from tests performed in laboratory, where the participants wearing the device and performing the tasks are in a supervised setting. This allowed contextualisation of the data (e.g. the participant in that specific moment was performing a squat test and the device was reporting that values). Currently, the device can collect data on the joint angulation through time, but it is difficult to interpret this data without a visual match of the task to what the participant is performing in that specific moment. To correctly interpret the data collected by the device, specific algorithms are required to analyse data in real time or post-download. The emerging field of machine learning and artificial intelligence in wearable technology (McLeod et al., 2016) may be a promising direction to move to

with the device, in order to make it smart enough to automatically differentiate among movement patterns and allow a deeper analysis of the data collected.

Despite the need for these improvements, the current prototype has shown promising results and further development will allow the device to be implemented in clinical trials to assess its reliability and suitability for its purposes. The device has potential in clinical applications and may be of interest for both researchers and clinicians interested in monitoring joint mobility in patients affected by joint impairments.

8.3. Future Research Directions

Directions for future research are recommended based on the findings and limitations of this thesis, in order to advance the clinical management of Perthes' disease and the understanding of the role that PA has on children with hip diseases.

1. *Define a standard tools set to measure the 14 outcomes reported in the defined COS:* Define the standard set of outcomes measurement tools following the COSMIN- Initiative guidelines. Because the 14 outcomes reported in the COS for Perthes' disease are still high in number, key tools including effective selection of PROM tools need to be outlined with the aim of having the fewest measurement instrumentations to measure the reported outcomes. This would facilitate researchers and clinicians in the tasks of collecting and reporting relevant outcomes, facilitating the adhesion to the COS proposed in chapter 5.
2. *International database on PA and sedentary behaviour in Perthes' disease:* Multi-centres from multiple countries measuring PROMIS and objectively measure PA and sedentary behaviour in Perthes' disease. This would provide

information on PA and sedentary behaviour in Perthes' disease globally and provide impetus for interventions aimed at improving mobility and reducing sedentary behaviour in these children.

3. *Wearable sensor validity study:* Repeat the study conducted in chapter 7 to include the final miniaturised version of the wearable sensor developed in chapter 6. This would provide objective measurement of the hip mobility during both clinical evaluation and daily living of the patients, and would allow effective comparison with the PROMIS questionnaire to seek for correlation between data obtained from the questionnaire and objective measurement obtained from the sensor. Additionally, assessment of the wearable sensor' readings during walking/climbing stairs in a gait analysis laboratory would allow to further compare the data acquired by the sensor to the data from the golden standard procedures (i.e. electric goniometer; gait analysis), and thus further validate the device.

8.4. Reflections on the Research Process

This thesis has employed different research methods (e.g. qualitative; quantitative) and disciplines (e.g. sport sciences; engineering) with the common aim to obtain an overview of the current practice and management of Perthes' disease and to develop and suggest new options to help researchers and clinicians in this area. Nowadays, a multidisciplinary approach to research topics is always more frequently adopted. The complexity of research questions and the needs of a more general overview that takes into account a variety of factors, direct the research process through a multi-levels collaboration among different experts and faculties. The work undertaken in this thesis has sought an overall approach to a complex condition such as Perthes' disease, taking

into account not only the perspectives of patients and surgeons, but a more combined view aiming to report the opinions, general feelings and expectations of these key stakeholders. The use of a multidisciplinary approach has been essential to the purpose of a more complete understanding of the findings. Indeed, this has enabled to quantitatively assess the degree at which Perthes' diseases physically affects the life of these children, while additionally discussing how these limitations in daily life and in recreational activities psychologically affect the child as well as the family's daily routine. The qualitative approach of this thesis has been highly valuable to rise outcomes of relevance for patients and their family, which had been not previously defined, suggesting the fundamental role that patients and caregivers' opinions have in properly direct clinical and research priorities. Appropriate space to children affected by Perthes' disease and their families has been given (Chapter 4) in order to let them not only contribute but be part of the core outcomes set defined in Chapter 5, helping clinicians and researchers to understand the best direction to follow when looking at treatments for Perthes' disease. The multidisciplinary collaboration with the Faculty of Engineering and Technology has been an additional step to move forward the results obtained in Chapter 5, and translates into practice new tools to assess some of the outcomes that were included in the final COS for Perthes' disease, leading to the development of the hip sensor prototype discussed in Chapter 6. Finally, the multidisciplinary approach to this work has also enabled to identify outcomes of relevance that were not previously assessed, such as the PA level of these children, of which investigation has been the starting point of Chapter 7. In this last study, the data collection involving qualitative (i.e. PROMIS) and quantitative (i.e. accelerometers) methods has given an insight onto the PA level of children affected by Perthes' disease (and other hip diseases), establishing also the correlation between the PA level and the

PROMIS scores of these children. These results may suggest the possible inclusion of the PROMIS questionnaire in a future core measurement tools set aiming to collect the outcomes of the COS defined in Chapter 5.

The multidisciplinary approach to this work has contributed to the novelty of the results, as well as to clear suggestions to direct further research in this area. Furthermore, aside the relevance for the aims of this thesis, the multidisciplinary approach here adopted has been a wonderful mean of personal growth for my research career. Being able to observe the topic of this thesis from different angles and being trained in skills that take advantages from the quantitative as well as qualitative method, made me understand the importance of a multidisciplinary approach to the research process, helping me developing a more critique mind when facing research questions. Additionally, the insight I had into the field of electronic engineering has surely changed my problem solving attitude and the approach I had into learning new and unknown disciplines. Thus, the multidisciplinary work conducted in this thesis has been surely beneficial for both the overall aim of the project as well as for my journey in becoming an experienced researcher.

8.5. Summary

The primary aim of this thesis was to understand and enhance the relevant core outcomes that should be measured in Perthes' disease. The defined COS of this thesis may be of interest in orthopaedic community when conducting clinical trials investigating the effectiveness of different interventions for Perthes' disease. Whilst further research is needed to define a standard measurement tools set to effectively assess these outcomes, the PROMIS questionnaire to assess mobility has shown to be employable to collect information on PA. Moreover, to objectively assess hip

mobility, more accurate instrumentation that can measure the joint mobility in the everyday environment of the child are required. The sensor described in this thesis has shown promise, but further development is required before it can be employed in clinical trials, which would provide feasibility data.

CHAPTER 9

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APPENDICES

APPENDIX A

Example draft of the Children's Booklet structure

HOW PERTHES AFFECTS

WHAT YOU DO AND HOW YOU FEEL

Dear Parent,

We are very interested in how Perthes' disease affects what your child does and how he/she feels. We have drawn up the following short booklet to help him/her to tell us, in his/her own words, how his/her bad hip affects what he/she does and how he/she feels.

Many thanks for all your help.

Introduction

This is a new booklet to help us find out how your Perthes' disease affects what you do and the way you feel. We have tried to make these questions as easy as possible to answer. Please try to answer all the questions. If you need your mum or dad to help you, that is fine.

In the tables on the next two pages, we are asking you what you can and cannot do and how you feel on a typical good day and a typical bad day. Please choose the smiley face that best matches how you feel or what you are able to do.

Answer	Meaning
	I am very happy; I can do what I want without any pain.
	I am quite happy; I can do most of what I want to but with some pain.
	It is okay; I could do some of what I wanted with some pain which sometimes got worse.
	I am quite sad; I cannot do most of what I want. I am in too much pain.
	I am very sad. The pain is very bad. I cannot do things and I normally do when I am not in so much pain.

Example:

On a good day, I was able to do everything I wanted to, play outside and with my friends.

Your answer might look like this.

On a bad day, I was unable to do what I wanted. The pain was too much. I could not go to school and just hoped some of my friends or my brother or sister might come and sit with me.

Your answer might look like this.

Now please turn to the next page of the booklet and try to tell us about the ways that your Perthes affects what you do and how you feel.

APPENDIX B

Parents Schedule

Introduction

- Thank you for agreeing to let me interview you….
- Gain informed consent for taping of the interview

The Questions

I would now like to ask you some questions about how your child's Perthes / hip problem is affecting what he is able to do day-by-day and also how his/her condition is affecting you and your family.

A. First of all, can you tell me the story of his/her condition, from when you first noticed any problem up to now?

Note for Interviewer: use the questions below as *prompts or to follow-up* on some aspect

OR

B. Use the following questions to guide/structure the interview. If you choose to do it this way:

- Begin by asking the parent to just say a little about their child (e.g. age, when first noticed a problem, when diagnosed … where now in treatment)
- Get a little information about the interviewee and their family (including age and gender of any brothers or sisters)
- Then, guide/structure the interview exploring/using the questions below

Role of Perthes in His/Her Physical Activity/Activities of Daily Living

1. Have you had to change his/her daily schedule and what he/she does?
   e.g. getting dressed, walking, playing….
2. Is there any activity he/she can no longer do, or has had to give up?

3. Can he/she lift heavier things, like he/she used to be able to?
4. How difficult is it for him/her to push, kicking a football, lift and carry heavy objects?
5. How far is your child able to walk without struggling, limping or feeling pain?
6. Does your child limp: Some of the time? All of the time? or Not at all?
7. Is the child able to sit for a long time in a chair? Sit on the floor?
8. Is his/her Perthes limiting his/her ability to play?
9. Is he/she able to ride a bike or scooter or roller skates?
10. How does his/her Perthes affect how well he/she sleeps at night?
    - When not in pain? and When in pain?

<u>Pain Specific</u>

1. Is your child in pain: some of the time? a lot the time?
2. Where is the pain?
    - Knee/ Hips/ Both / Elsewhere – if so where?
    - And what hurts the most?
3. How much pain does your child experience in their hip or other joints after activity?
    - On a good day? None A little Moderate Severe Very severe
    - On a bad day? None A little Moderate Severe Very severe

<u>Impact of Perthes on Pre-school/School</u>

1. Has he/she had to miss much pre-school / school because of his/her Perthes, and how much?
2. Was this because of:
    - Pain?
    - Diagnosis and treatment or other healthcare?
3. Can he/she sit cross-legged, for example, at school?
4. How does his/her Perthes affect what he/she does at pre-school / school? And, for example,
    - Are there limits around what he/she can and cannot do at pre-school/school, for example, PE class; go to the bathroom; play in playground?
    - Does his/her Perthes limit his/her taking part and doing sport and games?

- Can he/she change directions during any games or sport or other playing, for example, at play time and in the playground?

5. Does your child find it hard to pay attention at school?

Social Functions

1. How do your child's friends respond to the difficulties your child is experiencing? For example,
    - Do they come and sit with him/her or include him/her in their play or other activities when he/she is at pre-school / school?
    - Do they still come round to play with him?
2. Is his/her Perthes limiting his/her child's ability to take part in activities with his/her friends?
3. Has your child had to stop doing any hobbies because of hip pain?
4. Has your child taken up any new hobbies because of hip pain?

Emotional Functions

1. How does he/she feel about his/her hip problem? Does it make him/her feel:
    - Sad?
    - Afraid and a bit scared?
    - Frustrated, angry or cross?
2. Does your child worry about what will happen in the future?

General Health

1. How many medications / painkillers does your child have you to take daily due to their disease?
    - On a good day?
    - On a bad day?
2. How is your child's general health, apart from his Perthes?
    - Excellent Very Good Good Fair Poor
3. Does your child feel tired a lot of the time?

Effect on You and Your Family, including His Brothers and Sisters

1. How is his/her Perthes affecting:

- You?
- Your family?

2. How much of the time are you aware, and maybe change what you all do as a family, because of his/her Perthes?
    - How much of the time?
    - What did you used to do?
    - What do you do now?
3. How do you explain your child's condition to others?
    - Does it affect how they relate to him/her? Please give examples
4. Do you feel supported by:
    - Your GP?
    - Consultant?
    - Other healthcare practitioners, for example, his/her physiotherapist or any specialist nurse?
5. Do you worry about what will happen to him/her in the future and the treatment of his/her Perthes? Please tell more.

Now we would like to ask you about your greatest hope and worst fear for your child and his/her Perthes and its impact on his/her and you and your family's overall quality of life?

(a) My greatest hope is

……
……
……

(b) My worst fear is

……
……
……

Finally, is there anything else you would like to add, for example?

- *How it affects his/her quality of life?*

- *Anything else that particular importance or significance at the present time*?

That's it now! Thank you very much for your time and this information.

APPENDIX C

CONFERENCE PAPER - APPLIED HUMAN FACTORS AND ERGONOMICS, AHFE JULY 2019 (WASHINGTON DC, USA)

Note - The contents of this appendix were published in: **Leo D.G.**, Abdullah B.M., Perry D.C., Jones H. (2020) A Novel Joint Angle Measurement System to Monitor Hip Movement in Children with Hip Diseases. In: Ahram T. (eds) Advances in Human Factors in Wearable Technologies and Game Design. AHFE 2019. Advances in Intelligent Systems and Computing, vol 973. Springer, Cham.

A Novel Joint Angle Measurement System to Monitor Hip Movement in Children with Hip Diseases.

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Abstract. Children's hip diseases are an umbrella term to define different conditions (e.g. Perthes' disease; hip dysplasia) that affect the hip bone during the first months or years after birth. Assessing the degree of hip stiffness is important in the management of the disease, but to date there is no system able to continuously monitor hip angle in children. We aimed to characterize a novel wearable joint angle monitoring system able to collect data during the day in everyday life to assess hip mobility in children with hip diseases. We developed a flexible sensor embedded in a microcontroller based device, including an external SD card to store data. Preliminary data collected by the sensor shows its feasibility into monitor hip flexion/extension (SEM of ±0.20 degrees) during daily tasks. The preliminary results support moving forward with the prototype and improving its wearability, validating it in a wider study.

Keywords: optical flexible sensor · hip diseases · wearable technology · hip mobility

1 Introduction

Childhood hip diseases, including Perthes' disease and hip dysplasia, affect the femoral acetabular joint [1, 2] during the first months or years after birth with different grades of severity and symptoms. The two main characteristics of these hip conditions are pain and changes to normal range of motion (ROM) at the hip joint [1, 2]. The conditions induce stiffness of the hip joint, which causes difficulty in walking and affects normal daily life activities (e.g. climbing stairs or standing up from bed). Treatments for these conditions include surgery or conservative approaches, but common targets of the treatments are to manage the pain and to restore the normal hip mobility allowing a normal life in the affected children [1, 2].

The usual assessment of the impact of reduced mobility of daily life of these children is via quality of life questionnaires[3, 4], which indicates that hip stiffness reduces the ability to perform the daily tasks (i.e. limping and functional impairments during walking). However, there is no objective tool to measure functional joint mobility during daily living. In order to objectively assess the impact and extent of hip stiffness on the child's life a dynamic measurement instrument is required. This device could also be useful in monitoring disease progression and rehabilitation.

Nowadays, wearable technology is an emerging field in the health and medical sector (i.e. heart rate monitoring; body temperature measurement) [5, 6]. Despite this, no wearable instrumentation is available to monitor hip stiffness during daily life. Existing devices are only able to obtain hip ROM in a laboratory (i.e. electronic goniometers) or in clinical (i.e. manual goniometer) environment [7].

The aim of our study was to report the development of a wearable prototype for real-time wireless, continuous monitoring of hip ROM during everyday life, to be used as a monitoring tool in childhood hip diseases.

2 Developing of the Joint Angle Measurement Device

2.1 The Device

We developed a wireless device, with a core microcontroller (ATMEL ATMEGA328P), with 1 optical flexible sensor, to detect changes in hip motion (flexion/extension) (fig.1).

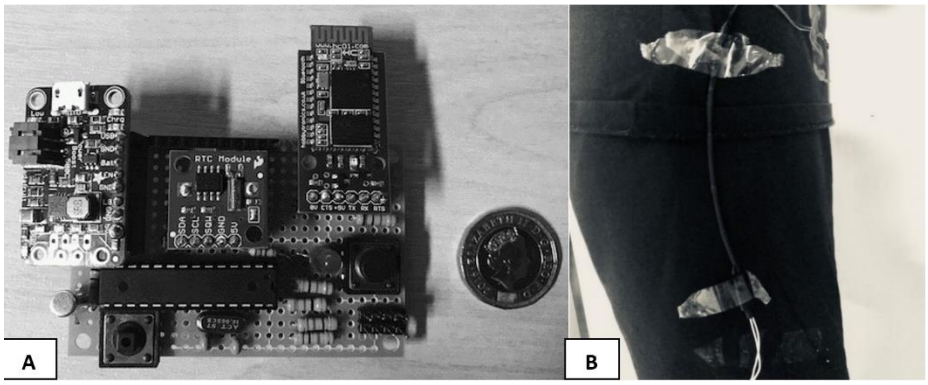

Figure 1: device prototype board (A) and optical flexible sensor attached over the clothes to the hip joint (B).

A Bluetooth interface (Tronixlabs HC-06) was implemented to send data for real time acquisition (Lab setting) to a computer. A local SD module (Hobby Components, HCARDU0008) for local data storage when the device is outside the laboratory environment; a real time clock microchip (Maxim Integrated, DS1307) for time and date recording; and a tilt ball rolling switch to detect changes in body position (person in standing or lying in down position), were also implemented.

The device runs at 5V and it is supplied by a 3.7 V lithium battery 2000 mAh (Adafruit), connected to a power booster (Adafruit PowerBoost500) to reach the running voltage.

The optical flexible sensor was structured as a variable resistor embedded in a voltage divider design. The sensor implements a light-emitting diode (LED) to one side of a plastic optic fibre (POF), and a light-dependent resistor (LDR) to the other side. The POF was isolated by external light interferences through an external coating made of black shrinking tubes. When the optical flexible sensor is bent, the changes in angle reflection of the light from the LED through the POF changes the amount of light received by the LDR. This induce changes in resistance, read by the device, allowing conversion of the resistance value to a change in angle (degrees).

The bending of the optical flexible sensor induces macro-bending loss of the light that causes the change in the amount of light received by the LDR. Kim and colleagues[8] report that when the angle (Θ) of incidence light in a POF is greater than its critical angle (Θ_c), the light is transmitted to the end of the POF through the total internal reflection. The critical angle is the incidence angle (Θ_i) when the reflective angle (Θ_r) of the light is at 90º of bending. Θi as showed in equation (2) can be directly obtained from equation (1):

(1)

$$\frac{n_1}{n_2} = \frac{sin\theta_2}{sin\theta_1} = \frac{sin\theta_r}{sin\theta_i} \quad (\theta_r = 90°)$$

(2)

$$\theta_i = sin^{-1}\left(\frac{n_2}{n_2}\right) = \theta_c$$

The light leak in the bent area when a POF is bended makes the angle Θ smaller than the Θ_c, inducing changes in light reflection through the POF and less light exposure to the LDR.

The changes in light exposure to the LDR (R1) increases it resistance, changing the output voltage (V_{out}) of the voltage divider connected to the micro-controller (with R2 as fix resistor) which reads the different output and convert it in different joint angle degrees, following equation (3):

(3)

$$V_{out} = V_{in}\left(\frac{R2}{R1+R2}\right) \qquad V_{in} = 5V$$

We set the value of R2 as a middle value between the minimum and the maximum value reached by R1 (in Ω).

In order to fit the subjective variation in hip mobility among subjects, the device self-calibrates itself in the first 15 seconds of recording. This is performed by the subject extending the joint in the 0º position (neutral hip flexion) and in the 90º flexion position.

2.2 Microcontroller's Code

Example pseudo code implementation of the voltage divider data acquisition from the microcontroller shown below (based on the example code made for flexible sensors implementations by Cates, Barton and Takahashi[9]):

```
#define flexion_PIN = *Input pin of the flex
                                sensor*;
const float VCC = 4.98;
const float R_DIV = *R1 VALUE*;
```

```
const float STRAIGHT_RESISTANCE = *R1 resistance
                                  when POF is straight*;

const float BEND_RESISTANCE = *R1 resistance when
                              POF is bended*;

int flexADC = analogRead(FLEX_PIN);

float flexV = flexADC * VCC / 1023.0;

float flexR = R_DIV * (VCC / flexV - 1.0);
```

3 Methods

Data obtained by the device were compared with a manual goniometer examine the accuracy of the measurements. The device and the manual goniometer were positioned statically at 0°, 45° and 90° of flexion. Measurements from the optical flex sensor were taken at a sample rate of 1 millisecond, for a period of 10 seconds for each angulation and then averaged.

Additional data were recorded using the device during dynamic movements that simulated daily activities such as sitting. The device was attached to the hip of the participant though medical tape (see Figure 1B) while the participant performed sit to stand manoeuvres on a chair.

4 Results and Discussion

4.1 Optical flexible sensor response

The optical flex sensor demonstrates linear relationship between the changes in LDR resistance made by the POF bending and the changes in angle detected by the device (Figure 2).

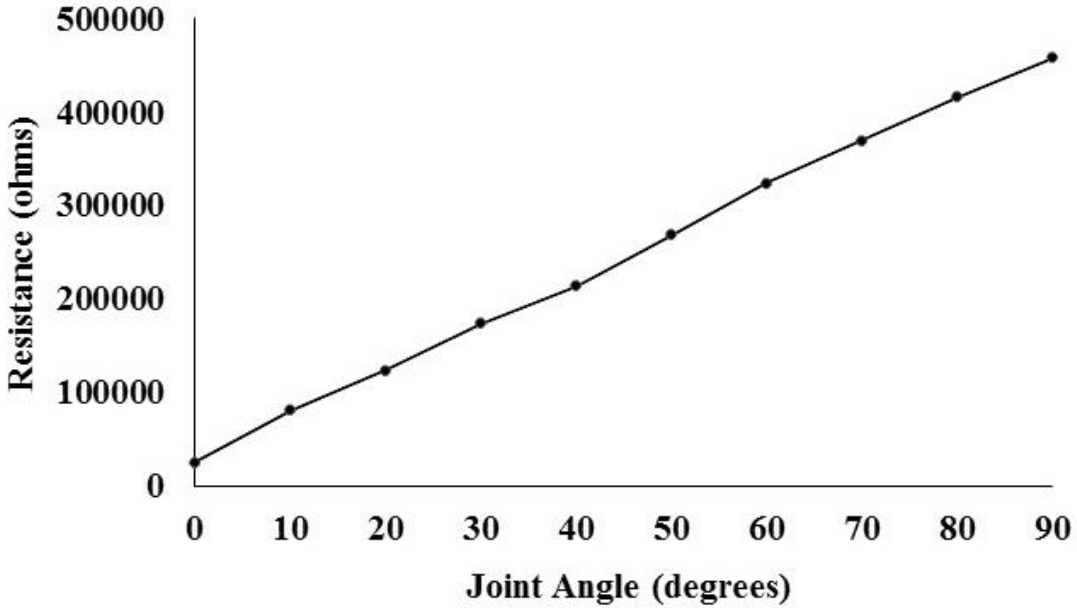

Figure 2: Linear relationship between changes in LDR resistance and device angle detection.

During the measurements taken in static position, the optical flex sensor shown good agreement with the manual goniometer at 0°, 45° and 90° of flexion (Table 1).

Table 1: Agreement in measurement in both devices at 0º, 45º and 90º.

Manual Goniometer Angle	Optical Flexible Sensor Angle Mean (±SEM)
0º	1º (±0.20º)
45º	44º (±0.20º)
90º	89º (±0.20º)

4.2 Example Tests Results

During 5 repeated trials the device was able to detect the expected hip flexion response while performing sit to stand manoeuvres (Figure 3).

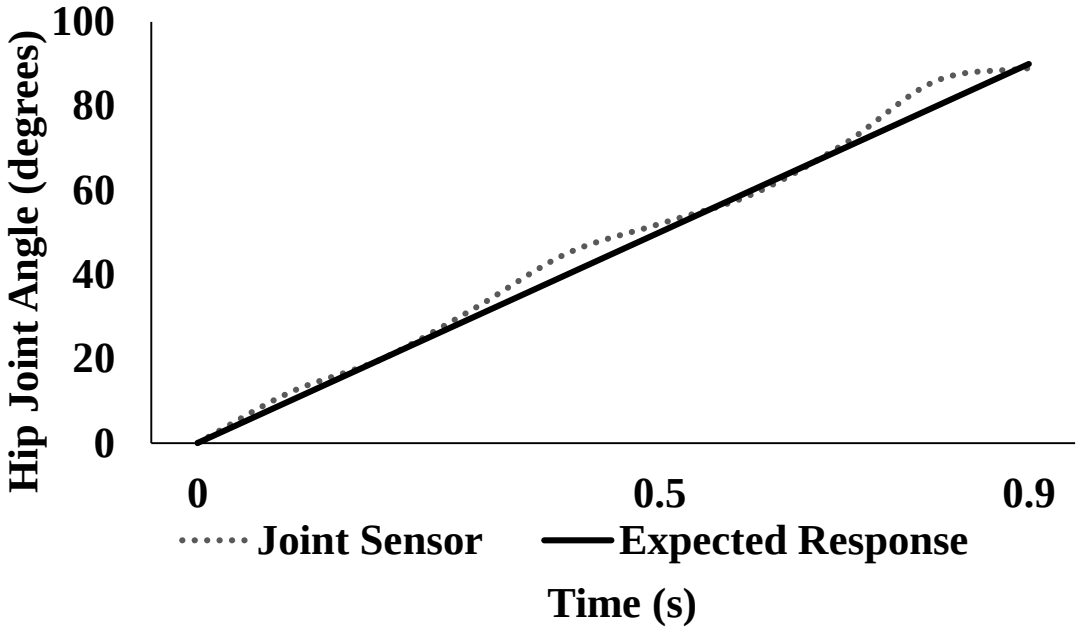

Figure 3: Changes in hip joint angle during body weight squat.

Taken together, this preliminary data show the device's ability to detect the changes in angle of the hip joint which reflect flexion and extension (relating to sitting and standing). The data were successfully transmitted to a computer/laptop (through the Bluetooth interface) or were stored on the SD card included in the device.

5 Conclusion

The aim of our study was to report the development of a wearable prototype for real-time, wireless, continuous monitoring of hip ROM during everyday life.

Our device has shown good preliminary results in the simulated daily activity tests performed, showing fast and accurate reading of the changes in the POF bending angle during flexion/extension of the hip joint. The preliminary data have shown the concept is feasible, In order to make the sensor suitable for implementation in clinical practice, further miniaturization and testing in ambulatory environments are required. Further modification will seek to improve the current prototype, improving its features and its wearability to fit the population of interest. Additional tests of reliability will be performed which include longer durations of data collection (i.e. 24 h/7 day period) using a larger sample size and including children.

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