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Leo, DG, Jones, H, Murphy, RC, Leong, JW, Gambling, T, Long, AF, Laine, J and Perry, DC (2020) The outcomes of Perthes' disease. Bone and Joint Journal, 102-B (5). pp. 611-617. ISSN 2049-4394

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The Outcomes of Perthes' (TOP) Study:

Development of a Core Outcomes Set for Clinical Trials in Perthes' Disease

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ABSTRACT

Aim: To identify a suite of the key physical, emotional and social outcomes to be employed in clinical practice and research concerning Perthes' disease in children.

Methods: The study follows the guidelines of the COMET-Initiative (Core Outcome Measures in Effectiveness Trials). A systematic review of the literature was performed to identify a list of outcomes reported in previous studies. Additional outcomes were sought, interviewing 12 children affected by Perthes' disease and 18 related parents, using a semi-structured interview format. Collectively, these outcomes 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. The International Perthes Study Group (IPSG) (Dallas, Tx – October 2018) discussed outcomes that failed to reach any consensus (either 'in' or 'out') before a final consensus meeting with representatives of surgeons, patients and parents.

Results: 23 different outcome domains were identified from the systematic review, and a further 10 from qualitative interviews. After round 1 of the Delphi survey, participants suggested 5 further outcomes domains. A total of 38 outcomes were scored in round 2 of the Delphi. Among these, 16 outcomes were scored over the pre-specified 70% threshold for importance (divided in 6 main categories: adverse events; life impact; resource use; pathophysiological manifestations; death; technical considerations). Following the final consensus meeting, 14 outcomes were included in the final Core Outcomes Set (COS).

Conclusion: COSs are important to improve standardization of outcomes in clinical research and to aid communication between patients, clinicians and funding bodies. We hope that the results of this study will be a catalyst to develop high quality clinical research to determine the optimal treatments from children with Perthes' disease.

KEYWORDS: Core outcomes set; Delphi; Perthes' disease; Legg-Calvé-Perthes' disease

INTRODUCTION

Perthes' disease (also known as Legg-Calvé-Perthes disease) is an idiopathic osteonecrosis of the femoral head in children [1, 2]. It is unclear what causes the disease, although socio-economic deprivation has been demonstrated to be the primary risk factor [3, 4]. Perthes' disease occurs five times more in boys than in girls, with a greatest incidence amongst white children in the UK and North Europe [2-5]. Symptoms of the disease include limping, stiffness of the hip joint and pain. Typical onset is between the ages of 4 and 8 years [1, 3].

Clinical management of Perthes' disease focuses on the prevention of the femoral head collapse and functional recovery (recovery of hip motion; reduction of pain) [6, 7]. 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 [8]. 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 [9].

Core Outcomes Sets (COS) represent consensus-derived minimum sets of outcomes to be reported in studies investigating a specific condition [10, 11]. By establishing a minimum set of outcomes to record, this will enable comparisons to be made between studies, and facilitate meaningful meta-analyses [11]. The use of COS is well-established through clinical research, though their adoption is somewhat slower in orthopaedic surgery.

The aim of our study was to identify, using the COMET-Initiative (Core Outcome Measures in Effectiveness Trials) guidelines, a suite of key physical, emotional and social outcomes to be employed in clinical practice and research into Perthes' disease.

METHODS

Systematic Review

We 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 [9]. 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 (Population Intervention Comparison Outcomes) 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 (DGL and WYL) who screened all the titles and abstract using Rayyan software [12]. 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 [9], 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 [11], 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 [13], not present in the original OMERACT filter, was also included.

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 elsewhere [14].

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 these outcomes using the same descriptors and with the possibility to change their scores if they wished to. Data obtained from round 2 were then summarised using the GRADE guidelines[15] 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).

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 (IPSG) 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. The only role of the IPSG was to give suggestions and guide the international representatives attending the final consensus meeting.

Final Consensus meeting

The list of outcomes obtained from the Delphi Survey was 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 independent 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 [16]), to ascertain those to include in the final COS.

RESULTS

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, we were unable to access the full text of 45 papers. Outcomes were sought from 112 papers. Figure 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 1).

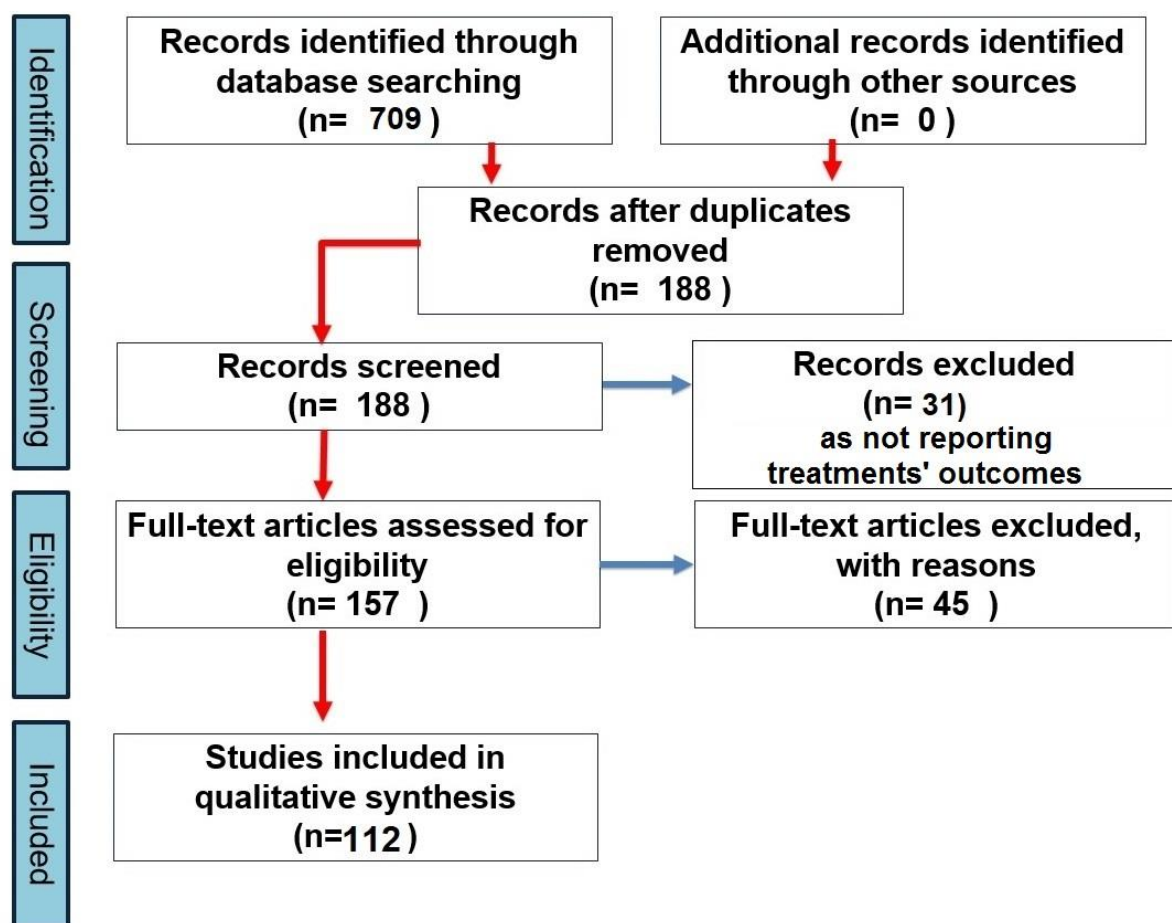


Figure 1: Prisma flow diagram showing papers identification and inclusion process.

Table 1: Systematic review outcomes categorised in domains (OMERACT modified filter).

Patients Reported Outcomes

10 outcomes not identified through the systematic review process were identified from qualitative interviews with parents [14] and added. The full list of the patient reported outcomes (PROs) obtained is reported in Table 2.

Table 2: PROs reported by patients and parents interviews.

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). 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). The total participants' attendance of round 2 was 62% of round 1.

Six additional outcomes were suggested after round 1 (Table 3) and included in round 2. Of the final 38 outcomes, 17 obtained "consensus in", 22 obtained "no consensus", and none

obtained “consensus out” after round 2. Table 4 shows the final list of the 16 outcomes that reached “consensus in” after the two rounds of the Delphi survey.

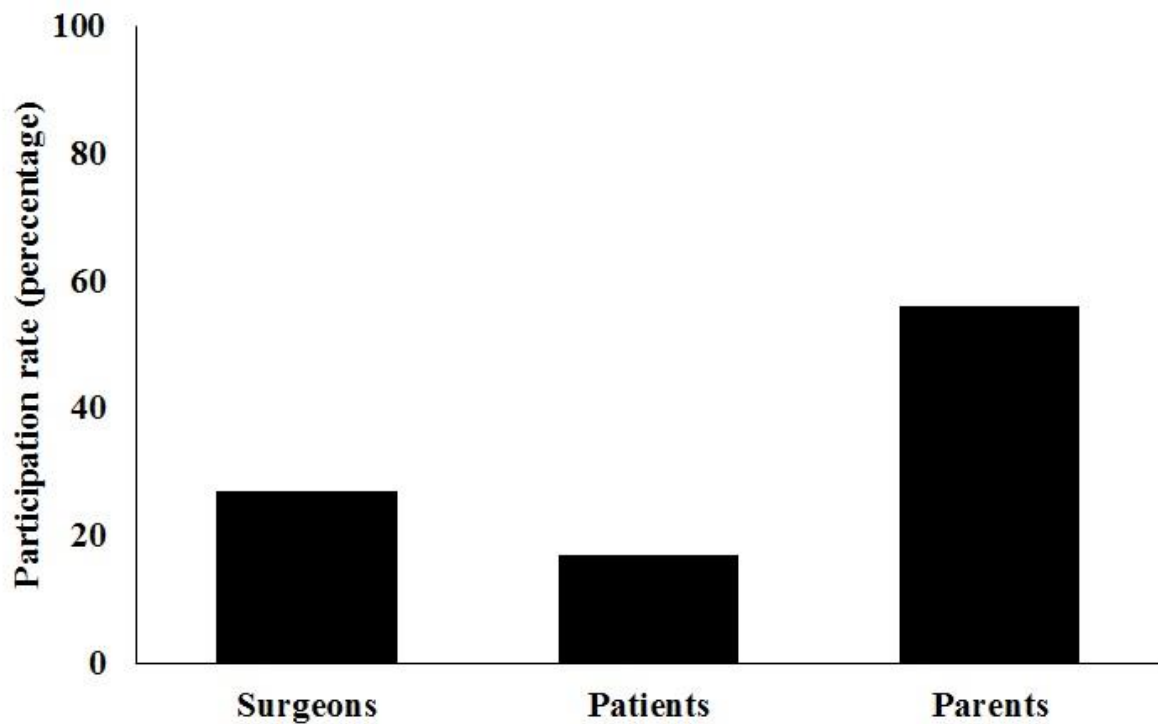


Figure 2: Participants’ distribution Delphi round 2.

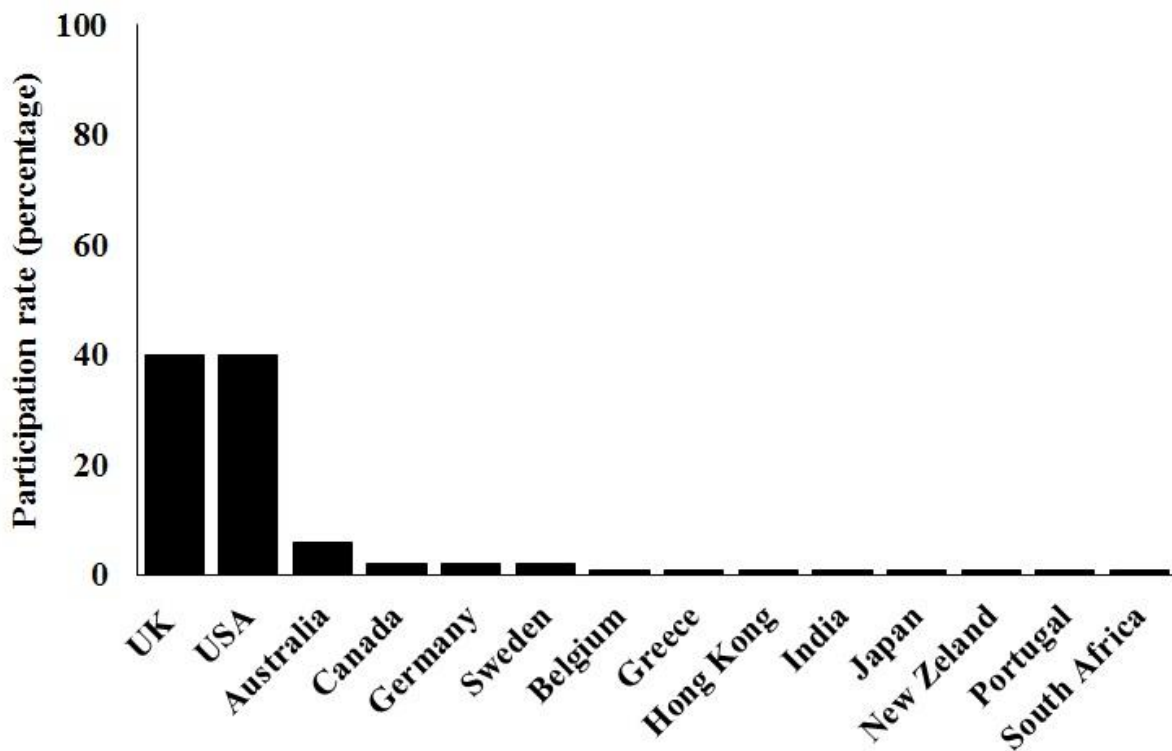


Figure 3: Round 2 Delphi survey participants' demographic data.

Table 3: Additional suggested outcomes after round 1 of the Delphi.

Table 4: List of the outcomes that obtained “consensus in” after round 2 of the Delphi.

IPSG Meeting Feedback

During the IPSG meeting, outcomes that did not reach any consensus (i.e. failed to reach either consensus ‘in’ or consensus ‘out’) during the two rounds of the Delphi process were discussed. From this discussion, notes were taken to the final consensus meeting for further final adjudication.

Final Consensus Meeting

Domain “Life Impact” - Nine outcomes reached “consensus in” during the Delphi Survey. Considering the large number of outcomes proposed, the final consensus group felt that three (sit comfortably; walking distance; and limping) could be broadly encapsulated under the heading of “activities of daily living”. Sport participation did not reach any consensus, but was subsequently voted “in” as this was thought to add functional information beyond activities of “daily living”. Three outcomes were added by participants during round 1 of the Delphi (weight gain; ability to climb stairs; use of walking aids), though these did not reach any consensus,

and were subsequently voted “out”. All other outcomes of the domain “Life Impact” that did not reach any 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 final consensus meeting because participants felt that this was captured through radiographic outcomes. The outcomes of this domain that did not reach any 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”, and felt that these were best combined to form a single outcome domain. Two outcomes did not reach any consensus during the Delphi Survey but were suggested to warrant particular further discussion by IPSG (overgrowth of great trochanter; articulo-trochanteric distance) however, these were voted “out” by the consensus group 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 any consensus during the Delphi survey but was voted “in” by the consensus group, and was included in the final COS. Other outcomes were voted “out” of the final COS.

Domain “Pathophysiological Manifestation” - “Hip mobility” did not reach any consensus during the Delphi Survey, and caused considerable debate on how this may be recorded. This was voted “in” by the consensus group, as it was felt that stiffness was a significant consideration in the progress of the disease. The documentation may be through formal measurement of hip movement, or through self-reported documentation of a limp (acknowledging that other components other than purely hip mobility may contribute to a limp). 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).

Table 5: List of the outcomes that reached “consensus in” to be included in the COS

DISCUSSION

We have developed a COS 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. We recommend 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 [11, 17], 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 [8]. It is therefore unsurprising that the management of Perthes' disease is one of the key research priorities in children's orthopaedic surgery [18].

The COMET initiative developed guidelines and standards to help maintain the quality of the COS development process [10, 11, 17]. Across medicine there are a wide range of COSs for different conditions (e.g. paediatric asthma) [19], however the orthopaedic community has perhaps neglected the importance of these [20]; with COSs available for only a few orthopaedic conditions (e.g. hip fractures) [21].

Our work has identified a list of core outcome domains to be measured and reported as a minimum in clinical research involving Perthes' 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 [6], 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.

Our 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 our study. The Delphi approach has been recommended as an ideal approach to identify outcomes of interest in clinical research [11, 22], yet ten different 'Delphi techniques' are reported, and given this variation the rigour of the process has been questioned [23]. The drop-out in participants' rate

it is a well known problem of the Delphi technique [24], and this has affected also our study with a response rate of only 62% of the panel during round 2 of the survey. However, unlike studies following up clinical participants longitudinally, drop-outs in this type of study design are unlikely to introduce bias [25]. A major strength of our work was to include qualitative interviews amongst affected children and families. We acknowledge 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. We acknowledge that the number of representatives attending the final consensus meeting was fewer than initially proposed [9], 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. We also acknowledge that the 14 outcomes proposed in the final COS are still a high number to be reported. Cochrane guidelines for systematic reviews suggest a maximum of 7 outcomes to be reported as this facilitates readers' understanding and retrieval of the review [26]. However, most of the outcomes proposed (e.g. activity of daily living; sport participation; pain) may be collected using only few Patient-Reported Outcomes Measures (PROMs) tools, and therefore seems both acceptable to patients and achievable.

In conclusion, our 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

we hope that this will be the catalyst to develop further clinical research amongst children with Perthes' disease.

DECLARATIONS

FUNDINGS

This work is funded by the Liverpool John Moores University and Alder Hey Children's Hospital. Additional support has come from the Perthes' Association UK.

ETHICS AND DISSEMINATION

Consultation with the Health Research Authority deemed this study a service evaluation project with no requirement for ethical approval (reference 60/89/81).

CONFLICT OF INTEREST

None of the authors has any competing interests. Any competing interests relating to any external reviewers will be declared in the final report. All correspondence should be sent to the team lead(s).

ACKNOWLEDGEMENTS

The following people contributed to the **TOP Consensus Meeting**: **Lisa Grant**, CEO Perthes Association UK (Guildford, UK); **Colleen Rathgeber**, MBA, Founder of the Legg-Calve-Perthes Foundation (Virginia, USA); **Jamie Kirkham**, PhD, Senior Lecturer in Medical Statistics, University of Liverpool (Liverpool, UK); **Alexander Aarvold**, MBChB, FRCSEd(Tr&Orth), Consultant Paediatric Orthopaedic Surgeon, Southampton Children's Hospital (Southampton, UK); **Adam Galloway**, MSc, Senior Children's Physiotherapist, Leeds Children's Hospital (Leeds, UK).

The authors want also to thank the members of the **International Perthes Study Group (IPSG)** and the **Perthes Association UK** for their support and contribution to this study.

AUTHORS' CONTRIBUTIONS

DCP, HJ and DGL conceived the study, and participated in its design. TG and AL designed the children questionnaire. TG, AL and RM designed the semi-structured interview's questions. DGL and WYL did the systematic review of the literature. DGL completed the semi-structured interviews with parents and the children booklet with the children. DGL, RM, TG and AL contributed to the design and analysis of the qualitative component. JL lead the discussion of the Delphi Survey at the IPSG. DCP, HJ, DGL and JL designed and conducted the final consensus meeting. DGL wrote the first draft of the manuscript. All authors edited the manuscript and read and approved the final version.

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Table 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

Table 2: PROs reported by the 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

Table 3: 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 4: 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

Table 5: The Definitive Core Outcome Set

Core Area	Core Domains	Outcomes
Adverse events	Adverse Events	complications of treatment
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	requirement for further surgery
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