■ EDITORIAL

The Non-Surgical Treatment Of Perthes' disease (Op NON-STOP)

THE JOURNEY TO A DEFINITIVE RANDOMIZED CONTROLLED TRIAL IN PERTHES' DISEASE

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Although Perthes' disease was first described more than 100 years ago,[1-3] and there has been a century of practice, there remains no high-quality evidence to guide its management. The lifetime risk in childhood is about one in 1,200, with males affected at least three times more commonly than females, and it predominantly affects children born in areas of deprivation.[4-6] The UK has the highest incidence of Perthes' disease worldwide, with about 500 new cases annually.[4] It has a profound impact on the quality of life of affected children, with patient-reported outcome measures (PROMs) comparable to, or even greater than, those seen in children with cancer.[7] Unsurprisingly, limitations in physical function have the main impact on quality of life.[8] Symptoms typically improve somewhat about three years after the diagnosis is made, once the hip is in the reossification stage of disease, although deformity remains in the long term.[8]

The management of Perthes' disease is controversial, although it remains focused on the principle of 'containment'. This involves the femoral head being encouraged to remain within the confines of the acetabulum, with the acetabulum 'containing' the structurally impaired femoral head, thereby controlling the direction of any collapse. It is believed that containment optimizes the shape of the femoral head, maximizing the congruency of the hip and preserving long-term function. However, there is uncertainty about how best to achieve 'containment' with, for instance, much variation in care throughout the UK.[9] The uncertainty principally involves the issue of whether early surgical containment is better than active non-surgical containment, which includes attempting to contain the hip with physiotherapy and modifications of activity. In light of these uncertainties, the British Society of Children's Orthopaedic Surgery and The James Lind Alliance Priority Setting Partnership identified the management of Perthes' as a top research priority, particularly identifying the need to understand the benefit of surgery compared with non-surgical care.[10,11]

While a randomized controlled trial (RCT) was undoubtedly the optimal approach, the organizations that fund large-scale research in the UK required reassurance that the clinical community could deliver challenging high-quality clinical research. Therefore, a simpler nationwide cohort study, called the British Orthopaedic Surgery Surveillance (BOSS) study, was first funded to explore the prevalence of the condition and the various forms of treatments.[8] Alongside this, clinicians in the UK began to organize RCTs in trauma, an area with seemingly less challenging uncertainty, showing their ability to deliver high-quality research in more common areas of orthopaedic surgery and traumatology.[12-15] The BOSS study and the clinical trials in trauma created a newly engaged nationwide clinical research community.

What did the BOSS study tell us about Perthes' disease? The BOSS study identified 396 patients with Perthes' recruited from 63 centres during an 18-month period.[8] There were large variations in treatment. No patients were treated surgically in some large hospitals, and many patients underwent surgery in others. When undertaken, the decisions about the timing of surgery were often informed by the age of the patient, the stiffness of the hip, and the degree of radiological collapse. However, decisions were frequently based on factors related to the surgeon rather than those related to the patient or the condition. The study's findings were that age, sex, and radiological collapse were prognostic of poorer radiological outcomes. This supports previous reports.[16,17] However, despite clinicians putting great emphasis on the 'stiffness' of the hip, this was found to have no bearing on the radiological outcome. Furthermore, and perhaps most importantly, there was also no evidence to suggest that 'containment' surgery influenced the radiological outcome. Nevertheless, this was an observational study and the choice to perform surgery was made by clinicians, maybe based on prognostic factors which are unknown or impossible to measure, such as clinical intuition. If children who were treated surgically in this study had not had surgery, the outcomes may have been even poorer, so the finding of 'no benefit' could be an error of indication bias caused by the observational nature of the study. However, if this argument is incorrect, there is much surgery being undertaken with no apparent benefit to children. The BOSS

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study therefore generated considerable interest and the wish for a definitive clinical trial in these patients,[8] to include being able to reassure the funders of the capability of the clinical community to deliver high-quality multicentre research.

A key challenge in developing a definitive high-quality RCT was to define the interventions.

It was shown in the BOSS study that containment surgery typically consisted of a varus osteotomy,[17] a shelf osteotomy,[18] or a Salter osteotomy.[19] With no evidence to suggest a difference between these approaches, a pragmatic approach to the design of such a RCT would be to include any containment procedure, and collect the details of each procedure that is undertaken. This could be performed with, or without, soft-tissue releases, preferably within four months of randomization. Postoperative care would follow the clinician's standard care with input from usual therapy services.

A non-surgical pathway required clarity, with evidence required to define the optimal package of care.[20] This was developed through a National Institute for Health and Care Research doctoral research fellowship, by a children's orthopaedic physiotherapist (AMG). Developing the Non-Surgical package (called NON-STOP: the Non-Surgical Treatment Of Perthes' disease) involved exploring the experiences of key stakeholders (clinicians and children with Perthes' disease and their families)[21] and undertaking a consensus exercise to establish an agreed optimal non-surgical treatment.[22] The NON-STOP intervention, which was agreed, involves a consultation with a physiotherapist, shortly after the diagnosis is made, in which a discussion focuses on the disease process, pain relief, modification of activity, and the necessity for walking aids. Patients are given access to supporting material to aid self-management, in the form of the NON-STOP app, a bespoke app for smart devices, and/or a physical workbook. The app/workbook outlines exercises in a child-friendly format, and seeks to address the concerns of families about the disease process, pain, activities, nutrition, and other aspects, and rewarding engagement with a modifiable avatar and stickers. A network of expert physiotherapists will be created, who will also support community physiotherapists.

However, the team psychologist was keen to caution against the idea of using the term "no surgery". In the same way that other trials have struggled with recruitment with an intervention group which has a negative connotation, the offer of something versus nothing is not seen as fair or appealing to patients or families.[23] In order to create a balance, with the assistance of parent co-investigators, the psychologist, and qualitative researchers, the non-surgical treatment is now called "active containment": keeping the child active without the need for surgery.

While radiological outcomes have traditionally been used to assess the progress of Perthes' disease, families have indicated that much more than a simple image is involved, with there being profound effects on the life of the child and their family. One family described anticipating the end of Perthes' disease as "waiting for the best day of your life".[21,24] Work with families has established a core outcome set to standardize the outcomes to be recorded in future high-quality studies of Perthes' disease.[25] This includes PROMs dealing with mobility, pain, quality of life, sleep, participation in education, as well as the radiological assessment of progression of the condition and the costs encountered by the families and healthcare system. These will be used in the Op NON-STOP study, with mobility being the primary outcome measure, given its impact on the child's life.

The definitive trial was conceived using this systematic approach. The Op NON-STOP study is a randomized, multicentre, superiority trial (ISRCTN 83315571). At least 216 children, aged five to 12 years, in the initial, sclerotic, or fragmentation stage of Perthes' disease, will be recruited. In order to ensure that the two groups are balanced for known prognostic factors, the patients will be stratifed by sex, age, and degree of radiological (lateral pillar) collapse, aided by a process called 'minimization'. We recognize that other factors, such as the Catterall classification[26] or 'head extrusion',[27] are often considered important. However, stratifying for an excessive number of variables complicates a trial, and randomization should ensure a balanced allocation of these characteristics across the intervention groups. Randomization will be between surgical containment and active containment using the NON-STOP intervention. The primary outcome measure will be the Patient-Reported Outcomes Measurement Information System (PROMIS) Mobility score at three years, collected with the other outcomes within the core set.[25] Patients will be followed up within the trial for 36 months from randomization for the primary outcome. Long-term follow-up is undoubtedly important, and the patients will be invited to join the Non-Arthroplasty Hip Registry (NAHR) at the completion of follow-up,[28] preventing any duplication of data collection during the trial.

In summary, many clinicians believe that Perthes' disease is too enigmatic a condition for a RCT to be designed and undertaken which would give useful outcomes. In our opinion, however, the Op NON-STOP study is an opportunity to prove how far clinical trials have developed, by delivering a definitive trial in a very difficult area to address one of the most important priorities of children's orthopaedic surgery worldwide.

The Op NON-STOP study began recruiting patients in November 2024, and we call on surgeons to give families the opportunity to help resolve the uncertainties about the treatment of this enigmatic condition.

Take home message

- The role of surgery versus nonoperative care in the management of Perthes' disease is a top research priority of children's orthopaedic surgeons worldwide.
- The Op NON-STOP study has been systematically designed, following a patient, intervention, comparison, and outcomes approach, to address this clinical uncertainty with support from families, research methodologists, and the children's orthopaedic and physiotherapy community.

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