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Comparison of brace to observation in stable, radiological developmental dysplasia of the hip: a protocol for a global multicentre non-inferiority randomised trial

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ABSTRACT

Introduction Brace treatment is common to address radiological dysplasia in infants with developmental dysplasia of the hip (DDH); however, it is unclear whether bracing provides significant benefit above careful observation by ultrasound. If observation alone is non-inferior to bracing for radiological dysplasia, unnecessary treatment may be avoided. Therefore, the purpose of this study is to determine whether observation is non-inferior to bracing for infants with radiological dysplasia.

Methods and analysis This will be a multicentre, global, randomised, non-inferiority trial performed under the auspices of a global prospective registry for infants and children diagnosed with DDH. Patients will be included if they present with radiological dysplasia (centred hip, alpha angle 43–60°, percent femoral head coverage greater than 35% measured on ultrasound) of a clinically stable hip under 3 months old. Patients will be excluded if they present with clinical hip instability, have received prior treatment or have known/suspected neuromuscular, collagen, chromosomal or lower-extremity congenital abnormalities or syndromic-associated hip abnormalities. Patients will be enrolled and randomised to undergo observation alone or brace treatment with a Pavlik harness for a minimum of 6 weeks. Follow-up visits will occur at 6 weeks, 1 year and 2 years post-enrolment. The primary outcome will be the norm-referenced acetabular index measured on the 2-year radiograph with a 3° non-inferiority margin. A total of 514 patients will be included.

The study is anticipated to start in April 2024 and end in September 2028.

The primary outcome will be compared between arms with a mixed-effects model with a random intercept for study centre, and a single covariate for the treatment group. If the lower bound of the 95% CI lies within 3° of the mean, we will treat this as evidence for non-inferiority.

Ethics and dissemination Ethics approval has been obtained from the lead site's ethics board (University of British Columbia, Children's and Women's Research Ethics Board). Ethics approval will be obtained from the local ethics committees or institutional review boards at each institution prior to patient enrolment. It is intended that the results of this study shall be published in peer-reviewed journals and presented at suitable conferences.

Trial registration number NCT05869851.

STRENGTH AND LIMITATIONS OF THIS STUDY

⇒ This study will be a large randomised controlled trial to investigate whether observation is non-inferior to bracing for the treatment of radiological hip dysplasia in infants; it will provide clinicians with important information as to whether unnecessary treatment can be avoided.
⇒ The non-inferiority study design with small non-inferiority margin will be powered to detect small but meaningful differences in acetabular index.
⇒ The results of this study will be generalisable to the majority of children with radiological dysplasia due to the global involvement of 27 sites from eight countries.
⇒ A strength of this study is the pragmatic design which increases the feasibility for recruitment and enables participation from sites from around the world.
⇒ The pragmatic design of the trial is also a limitation as there is a degree of subjectivity in the parameters for crossover between the treatment groups and time in brace per day has not been standardised.

INTRODUCTION

Developmental dysplasia of the hip (DDH) is the most common paediatric hip disorder, affecting an estimated 1%–3% of all infants.[1] DDH represents a spectrum of disorders, ranging in severity from mild dysplasia in a clinically stable hip, to complete hip dislocation. If left undetected or untreated, it can lead to debilitating complications later in life.[2 3] Much of the existing evidence in the literature is from retrospective or single-centre studies and the spectral nature of the disorder has led to confusion in diagnostic

terminology, as well as inconsistencies in treatment and management.

There is consensus that early diagnosis is critical to optimise outcomes and mitigate long-term disability for children. However, discrepancies in screening and management practices are abundant. Clinical hip examinations should be performed on all newborns. Some countries or health regions employ universal ultrasound screening in addition to the clinical examination.[4–7] Other countries/regions employ selective ultrasound screening based on specific DDH risk factors; namely, breech presentation, family history of DDH and history of clinical instability.[8–11] Regardless of the screening programme, missed or late presentations still occur, warranting further investigation.[12–15] In contrast, there is also concern over the potential to overtreat, particularly with universal ultrasound screening. The natural history of DDH appears to be dependent on both the type and severity of the hip abnormality, with mild dysplasia often resolving without any evident clinical manifestation,[16] at least in childhood. Most natural history studies indicate that the majority of DDH cases discovered by clinical examination or imaging study in newborns represent hip laxity and immaturity.[17] Specifically, 60%–80% of clinically identified abnormalities and 90% of ultrasonographic abnormalities spontaneously resolved without treatment in early infancy.[17] These findings raise important questions regarding treatment decisions, including the potential to over-treat hips that may self-correct, optimal treatment timing and course of treatment action. In contrast, severe dysplasia can present clinically during infancy and adversely impact healthy hip growth and development extending through childhood into adulthood. Interventions to ameliorate the natural history of DDH have depended on the severity of dysplasia and on the age of diagnosis or presentation. Bracing during infancy can be an advantageous treatment option; however, more drastic manipulative or surgical measures may be necessary as severity or age advances.

In a randomised controlled trial, Wood *et al* examined the impact of abduction bracing on clinically stable but sonographically dysplastic hips, as measured by acetabular coverage at 2–6 weeks of age (trial start) and 3–4 months of age (trial end).[18] A total of 63 hips in 44 infants were randomised to abduction bracing or observation for 3 months. The observed cohort (18 hips) were examined to provide insight on the natural history of acetabular coverage, which was found to increase from 36.7% at birth to 48.6% at 3 months in the absence of any treatment. While improvement in acetabular coverage was significantly better in the splinted group (32.8% to 54.3%), there was no appreciable difference in the acetabular index (AI) between the two groups as measured on plain radiograph at 2 years of age. The America Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guideline cited this study to provide a limited recommendation for observation over bracing in this patient cohort.[17]

A more recent prospective cohort study by Kim *et al* examined the treatment patterns for radiologic dysplasia among surgeons at a single centre.[19] A total of 107 hips in 80 infants diagnosed with ultrasonographic dysplasia were included, with 65 hips treated by Pavlik harness and 42 hips observed alone. Ultrasonographic findings related to femoral head coverage (FHC) and alpha angle at diagnosis significantly influenced the treatment decision in this study. At 2-year follow-up, 87% of Pavlik harness-treated hips and 93% of observed hips achieved a good radiographic outcome. Most recently, a randomised control trial (RCT) from five centres across the Netherlands reported comparable outcomes between Pavlik harness and active surveillance.[20] Infants included in this study were between 3 and 4 months of age, and the primary outcome of this was the alpha angle on ultrasound at 6 months.

Brace treatment for approximately 6 weeks is common to address radiological dysplasia; however, it is unclear whether this approach provides significant benefit above careful observation by ultrasound. While a conservative, less costly approach, brace treatment is not without potential complications and drawbacks. There are still substantial healthcare costs and resources associated with brace treatment, but there is potentially an under-recognised psychosocial cost in regard to preventing or disrupting mother–infant bonding in the newborn period.[21] Coping with the difficulties of brace treatment can be stressful for families, particularly mothers of newborns, but the ultimate psychosocial impact has been under-researched to date. There is evidence to suggest that events occurring during establishment of breastfeeding may impact the mother's ability to breastfeed.[22] The UK Hip Trial also found that maternal anxiety and worries about their infant's hip were increased with early brace treatment, but were not elevated by ultrasound monitoring in isolation.[23] Furthermore, bracing can present challenges to daily family life, including dressing, mobility and the need for specialised furniture, car seats and other equipment. If observation alone is non-inferior to bracing for radiological dysplasia, unnecessary treatment may be avoided, potentially decreasing both the psychosocial impact of disrupted mother–infant bonding and needed healthcare resources and costs.

Rigorous multicentre randomised controlled trials are required to appropriately address this question with relevance to a global patient population and provide a strong recommendation for care. The limited existing literature compels a better understanding of the natural history of radiologically dysplastic hips to inform more consistent guidelines backed by the substantial evidence generated by a well-executed, international, multicentre RCT.

Objectives and hypotheses

We propose to utilise the existing collaborations and infrastructure of the Global Hip Dysplasia Registry (GHDR) and leverage our collaboration with a group in the Netherlands performing a similar Treatment with Active Monitoring (TRAM) trial to determine whether observation alone is sufficient for infants with clinically

stable radiologically abnormal hips. Specifically, we aim to:

1. Determine whether observation is non-inferior to bracing for infants with radiological dysplasia.
2. Provide a strong recommendation for management of this subset of DDH patients.
3. Compare findings to those of the Netherlands trial, which is being carried out in older patients (10–16 weeks at diagnosis).

We hypothesise that observation of infants with radiological abnormalities of the hip joint will be non-inferior to brace treatment, as adjudged by AI at 2-year follow-up.

METHODS AND ANALYSIS

Study design and setting

This study will utilise the established infrastructure of the GHDR. GHDR was established in 2016, aimed at collecting longitudinal data on infants and children across the entire DDH spectrum.[24] This specific trial will function as a targeted substudy within the more extensive registry, and is a global multicentre, prospective randomised non-inferiority trial designed to evaluate the necessity to treat infants with radiological hip dysplasia. Currently, 27 sites from eight countries (Australia, Brazil, Canada, India, New Zealand, Pakistan, the UK and the USA) have agreed to participate and randomise eligible patients (table 1). The study is anticipated to start in April 2024 and end in September 2028.

Table 1 Site involvement and location

Country	Site name
Australia	University of Adelaide, Adelaide
	Queensland Children's Hospital, Brisbane
	Royal Children's Hospital, Melbourne
Brazil	Universidade de São Paulo, São Paulo
Canada	BC Children's Hospital, Vancouver
	Children's Hospital of Eastern Ontario, Ottawa
	Royal Columbian Hospital, New Westminster
	Shriners Hospitals for Children—Canada, Montreal
	The Hospital for Sick Children, Toronto
India	Bai Jerbai Wadia Hospital for Children, Mumbai
	Ganga Medical Centre & Hospitals Pct., Coimbatore
	Kasturba Medical College, Manipal
	Sancheti Institute, Pune
New Zealand	University of Otago, Otago
Pakistan	MTI-Khyber Teaching Hospital, Peshawar
UK	Royal Aberdeen Children's Hospital & Woodend Hospital, Aberdeen
	University of Southampton, Southampton
	Royal Hospital for Sick Children, Edinburgh
USA	Arnold Palmer Health Centre, Orlando
	Children's Hospital of Philadelphia, Philadelphia
	Hospital for Special Surgery, New York
	Lurie Children's Hospital, Chicago
	Nemours Children's Hospital, Wilmington
	Nicklaus Children's Hospital, Miami
	Rady Children's Hospital, San Diego
	Texas Children's Hospital, Houston
	Texas Scottish Rite Hospital, Dallas
	The Stanford Child & Adult Hip Preservation Centre, Stanford

Inclusion criteria

- Patients presenting with radiological dysplasia of a clinically stable hip under 3 months (12 weeks) of age.
- Radiological dysplasia will be defined as a centred hip with an alpha angle between 43° and 60° and a percent FHC greater than 35, as measured on ultrasound examination.

Alpha angle parameters were chosen as an alpha angle below 43° indicates severe dysplasia likely requiring treatment, while an alpha angle of 60° or above represents a normal hip in this patient age cohort if the hip is centred.[25] FHC parameters were chosen based on the cumulative findings of multiple studies seeking to define what per cent FHC constitutes a hip dislocation. Striano *et al* documented that the 90th percentile of a prospective cohort of 325 Ortolani positive (clinically dislocated) hips was 33% FHC,[26] while Terjesen *et al* found an average 35.7% bony rim percentage in a small cohort of seven Ortolani hips.[27] Similarly, Holen *et al* have reported ranges of 33%–37% mean FHC in Ortolani positive hips,[28] and Novais *et al* documented a median FHC of 23% in a cohort of 78 Ortolani positive hips.[29] Striano *et al* concluded that a dislocated hip could reasonably be defined as FHC≤33%;[26] thus, in the absence of clinical any instability, an FHC greater than 35% could reasonably represent isolated radiological dysplasia.

Exclusion criteria

- Patients presenting with radiological dysplasia older than 3 months (12 weeks) of age.
- Patients presenting with clinical hip instability (Ortolani or Barlow positive).
- Patients with known or suspected neuromuscular, collagen, chromosomal or lower-extremity congenital abnormalities or syndromic-associated hip abnormalities.
- Patients who received prior treatment (ie, Pavlik harness) for DDH.

Patient enrolment and randomisation

Patient eligibility will be determined by their treating clinician and parents of patients who meet inclusion criteria will be offered enrolment by the research team in both this RCT and the more extensive registry (GHDR). Parents may provide informed consent to either one or

both options should they choose. The central team statistician will generate a randomisation schedule and randomisation will occur through the Research Electronic Data Capture (REDCap) randomisation module. Randomisation will be blocked in randomly varying sizes of four, six and eight, and stratified by trial centre and sex. As DDH is five times more common in girls than boys, we will stratify by sex to ensure an equal distribution in each group. Enrolled patients will be randomised into either the brace treatment or observation arm. Parents not wishing for their child to be randomised will be offered enrolment in an observational cohort arm of the study and complete the same follow-up as the randomised cohorts.

Trial interventions

Following randomisation, the control group will undergo observation (active monitoring) only while the experimental group will be treated with a Pavlik harness for a minimum of 6 weeks. All clinic personnel involved in the application of the Pavlik harness will undergo training via a validated, simulated learning module to ensure uniformity in harness application across all centres.[30] Parents will also receive training via the clinical care team to ensure accurate use of the harness throughout the treatment period. Both the control and experimental groups represent current standard of care treatments for infants diagnosed with radiological dysplasia as there is a lack of consensus as to whether this form of DDH will resolve spontaneously or requires active treatment. Treatment in a brace beyond 6 weeks will be allowed in the experimental group as determined by the treating physician's standard of care for their practice and clinical expertise.

Throughout the trial, patients in the observation arm will be closely monitored to determine if they need to crossover to the brace treatment arm. If radiological parameters have deteriorated at the 6 week ultrasound, brace treatment will be initiated and maintained as necessary. The decision to begin brace treatment in the observation group will be left up to the treating surgeon, but one of the following criteria must be met: (1) the hip becomes decentred (unstable); (2) ultrasonographic parameters deteriorate from baseline (3) ultrasonographic parameters do not show sufficient improvement over a period of at least 1 week.

Data collection

Each site will collect and enter deidentified data into a REDCap database. Data will be queried from the database and checked for illogical data by the central coordinating site. Each participating centre will have access only to its own patient information or code lists. Patients in both the brace and observation arms will be monitored according to each centre's standard of care protocol, with minimum mandatory study follow-ups of a 6 week postenrolment ultrasound, and 1-year and 2-year postenrolment pelvic radiographs. Some centres participating in the trial perform weekly ultrasound as standard of care, and that data will be collected where applicable in addition

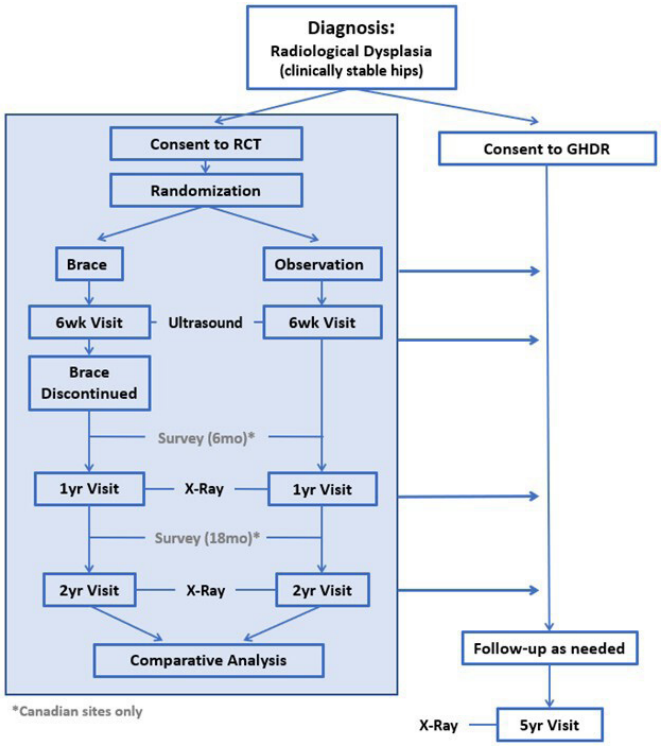

Figure 1 Study timeline flow chart. GHDR, Global Hip Dysplasia Registry; RCT, randomised control trial.

to mandatory study visits. The 2-year follow-up represents the endpoint of the RCT, at which time those patients who were also enrolled in the more extensive registry (GHDR) will continue to be followed according to standard of care until skeletal maturity. Any event requiring intervention, either clinical or surgical, will be captured with collection of radiographic imaging, clinical and surgical information. The complete study timeline is shown in figure 1.

A summary of the data to be collected at each visit is included in table 2.

Primary outcome

The primary outcome measure is the norm-referenced AI measured on a 2-year radiograph. The AI provides a measure of the steepness of the acetabular roof. An AI<20° is considered normal at age 2, while an abnormally high AI is associated with DDH, and more specifically with acetabular dysplasia. The AI will be measured on the 2-year radiograph by an assessor blinded to the patient's assigned group, and AIs will be compared. Measurement error in AI has been shown to be 5°;[18] however, a more recent study demonstrated good-to-excellent inter-rater and intrarater reliability in AI measurement.[31] Thus, 3° has been empirically chosen to represent a margin of non-inferiority (ie, the single radiograph at 2 years will be considered no worse than bracing should the AI be <3° higher in the observation patient group). All radiographs will be measured by two independent, blinded assessors at the central coordinating site following consensus discussion on measurement technique. We will use the

Table 2 Data collection at each study visit

Outcome measures	Study visits*							
	Screening/ baseline (day 0)	6 weeks (±2 weeks)	6 months† (±1 month)	1 year (±2 months)	18 months† (±1 month)	2 years (±2 months)	5 years (4+ years)	Additional visits§ (as per standard of care)
Screening and consent	X							
Randomisation	X							
Demographics	X							
Bracing details¶	X	X						X
Clinical assessment	X	X		X		X	X	X
Ultrasound measurements	X	X						
X-ray measurements				X		X	X	X
Parent/guardian satisfaction		X		X		X		
Parent/guardian perception		X						
EuroQol-5D VAS		X		X		X		
Healthcare resource use†		X	X	X	X	X		
Surgical/non-surgical intervention details**		X		X		X		X

*Timing of visits are calculated from the day of enrolment (day 0).
†Only required for Canadian centres.
‡Only for participants also enrolled in GHDR.
§Conducted as needed or according to the local standard.
¶Required for participants randomised to the brace treatment group.
**Only as needed.
VAS, visual analogue scale .

average of the assessors' measurements; however, discrepancies>2° will be reassessed.

Secondary outcomes

1. Ultrasound parameters including alpha angle, beta angle and per cent FHC will be collected for both brace and observation groups and assessed by blinded assessors at the central coordinating site.
2. Complications including development of femoral nerve palsy or avascular necrosis, progression of DDH (defined by worsening AI based on age-based standards, and/or increasing International Hip Dysplasia Institute (IHDI) grade) and need for further treatment (such as prolonged brace treatment, closed or open reduction and other surgeries), will be recorded by research staff at each visit and through chart review.
3. Parent/guardian perceptions of caring for and bonding with their child will be assessed using a parent/guardian-reported 16 question survey.
4. Parent/guardian quality of life will be assessed using the visual analogue scale (VAS) component of the EuroQoL-5D (EQ5D) completed by parents/guardians.
5. Parent/guardian satisfaction with their child's treatment/care will be assessed using a VAS.
6. Healthcare resource use will be assessed at all Canadian participating centres through a parent/guardian-reported questionnaire at each visit and through chart review. The questionnaire will collect information about additional visits and testing outside those required as part of the RCT including visits to healthcare professionals; radiographs, ultrasounds and other imaging; medication use and additional treatments related to the participants' diagnosis of DDH. The questionnaire will also collect out-of-pocket costs to families.
7. As this trial is planned to take place within the existing GHDR registry, participants will be followed up (where possible) beyond the trial end date. In those patients with available data, we will compare centre-edge angle (CEA) and AI at 5 years for non-inferiority. These analyses will include adjustment for variables and treatments occurring between the end of the trial and the 5 year follow-up that may affect the CEA or AI.

Statistical analysis plan

All primary analyses will be performed following the intention-to-treat principle. All baseline and relevant centre and demographic information will be summarised between trial arms via appropriate summary statistics (medians and IQRs for continuous variables and counts for categorical variables).

Primary outcome

The primary outcome will be compared between arms with a mixed-effects model to account for nesting within study centre, repeated measurements between multiple raters (random-effects) and covariates for sex and treatment group (fixed-effects).[32] The coefficient for the treatment arm in this model represents the estimated mean difference between groups and will be reported with a 95% CI. To assess non-inferiority, we will use the lower bound of the 95% CI from the mixed-effects model. If this bound is less than 3°, we will treat this as evidence for non-inferiority.

Secondary outcomes

Six-week ultrasound metrics will be compared similar to the primary outcome and the estimated mean difference between groups will be reported with a 95% CI. Adverse events will be summarised by incidence proportion and a time-to-first-event analysis will be conducted using Kaplan Meier estimators. The number of patients in the non-brace arm requiring subsequent bracing and time-to-bracing will also be reported. Aggregate scores from the parent perception and satisfaction questionnaires and EQ5D-5L will be compared between trial groups.

Economic evaluation

We will perform cost-effectiveness analyses from healthcare payer and societal perspectives over 2 years. Incremental cost-effectiveness ratios will be calculated as cost per additional pathologic hip (AI>20°) avoided. We will use the net benefit regression (NBR) framework[33] to estimate the incremental net benefit (INB) of brace treatment where brace treatment will be considered cost-effective if the INB is positive. We will perform the NBR from both perspectives using willingness to pay values varied between $0 and $50 000 per pathologic hip avoided. To characterise the uncertainty around our estimate of INB, we will calculate 95% CIs and cost-effectiveness acceptability curves to assess precision of estimates.[34] Costs and effects accrued beyond 1 year will be discounted at a rate of 1.5%.[35]

Combined GHDR and TRAM (Netherlands) trial analysis

Following completion of both our trial and the TRAM trial, results will be pooled to compare the primary outcome across all age groups included in the two trials. This combined analysis will enable the determination of any age-related impact on the effectiveness of active monitoring compared with brace treatment. We will also compare ultrasound parameters at enrolment and 6 weeks postenrolment in infants less than 12 weeks versus infants 12–16 weeks old. This comparison will enable us to determine whether there is evidence for natural improvement, and whether the age at which active monitoring or brace treatment is instated influences the time to hip normalisation.

Sensitivity analyses

Effect modification of the comparability in the primary outcome between groups will be assessed by including relevant baseline risk factors in the above regression model. Sensitivity analyses will include (1) the addition of a priori identified patient and centre level covariates thought to impact the primary outcomes and (2) multiple imputations for missing outcomes due to possible differential follow-up between groups. Variables considered for adjustment and effect modification include patient age, treating surgeon, alpha angle (from ultrasound) and FHC at baseline. Continuous variables for adjustment may be treated with non-linearities if needed, and age will be categorised as 0–3, 3–6, 6–9 and 9–12 weeks for the purpose of studying effect modification. If considerable heterogeneity exists between treating surgeons, an additional sensitivity analysis including this as a nested random effect (within centre) will be conducted. Finally, a per-protocol analysis will be conducted including only those in the non-brace arm that do not subsequently require bracing. This analysis will be adjusted for relevant confounders (as listed above), using best-practice methods.[36]

Observational data

Those patients choosing not to enrol in the trial will still be followed up for the outcomes listed above where possible and be included as an observational cohort. The analyses conducted above will be repeated on (1) this observational cohort only, and (2) combining the trial and observational cases. In both cases, as some patients will not be randomised, models will be adjusted for potentially imbalanced confounders of the treatment choice/outcome relationship. This adjustment may include either direct adjustment in the above regression models, or the use of propensity score methods if appropriate.

All analyses will be conducted using R statistical software, and a significance level of 0.05 will be used for the primary outcome analysis.[37] All analyses will be outlined in detail in a statistical analysis plan and signed off by investigators prior to any data analysis. The analysis plan will accompany the final publication of results.

Sample size

A single-centre trial to estimate a non-inferiority margin of 3° with 90% power at a significance level of 5% and assuming a 20% loss to follow-up would need a total of 193 patients per arm assuming a SD of 3°, and a true difference between active monitoring and brace treatment of 2°.[38 39] Due to expected moderate between-site heterogeneity (assumed coefficient of imbalance of 0.75),[40] we estimate a needed increase to 257 patients total per arm.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

ETHICS

Ethics approval has been obtained from the lead site's ethics board (University of British Columbia, Children's and Women's Research Ethics Board). Ethics approval will be obtained from the local ethics committees or institutional review boards at each institution prior to patient enrolment.

DISSEMINATION

While we will not make individual participant data available for this study, we do intend to disseminate study results to participants, researchers and the broader public. It is intended that the results of this study shall be published in peer-reviewed journals and presented at suitable conferences. We also intend to prepare plain language summaries and visual/video abstracts of study results, which will be emailed to participants (those whom provided consent for email contact). These visual abstracts will also be posted to our lab's social media accounts, as well as that of our supporter, the I'm a HIPpy Foundation, who works closely with our patient and family community.

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Contributors ES and BOZ initiated and designed the study and wrote the protocol and manuscript. KM and SK contributed to the design of the study and review of the manuscript. JNB and VN designed the analysis plan and contributed to the writing of the protocol and manuscript. ES is the guarantor of this manuscript. The GHD Study Group contributed to the design of the study and critical reading and approving the protocol and manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

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