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Complete List of Authors:	Schaeffer, Emily; The University of British Columbia Faculty of Medicine, Orthopaedics; Zomar, Bryn; The University of British Columbia Faculty of Medicine, Orthopaedics; BC Children's Hospital, Orthopaedic Surgery Chen, Maio; AO Foundation, ITC Mulpuri, Kishore; University of British Columbia, Department of Orthopaedics; International Hip Dysplasia Institute, Joeris, Alexander ; AO Foundation, AO ITC PedOrtho, Study Group; Not applicable
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TITLE

Management of long bone fractures and traumatic hip dislocations in pediatric patients: A prospective multicenter observational cohort registry

Bryn Zomar[1], Maio Chen[2], Emily Schaeffer1, Kishore Mulpuri[1], PedORTHO Study Group, Alexander Joeris[2]

[1]: Department of Orthopaedics, The University of British Columbia; BC Children's Hospital, Vancouver, Canada

[2]: AO Foundation Innovation Translation Center, Davos, Switzerland

Contributorship: E. S., K. M., and A. J. initiated and designed the study and contributed toward the writing of the protocol and the manuscript. B.Z. and M.C. contributed toward the writing of the protocol and the manuscript. All members of the PedORTHO Study Group contributed toward the design of the study and critical reading and approval of the protocol and manuscript. E. S. is the guarantor of this manuscript.

ABSTRACT

Introduction

Management controversy and clinical equipoise exists in treatments of long bone fractures and traumatic hip dislocation in pediatric patients due to the lack of high-quality clinical evidence. This protocol describes the effort of a large prospective global multicenter cohort study (registry) aiming at providing quality data to assist evidence-based treatment decision-making.

Methods and analysis

Eligible pediatric patients (N=750–1000) with open physes suffering from proximal humerus fractures, distal humerus fractures, proximal radius fractures, forearm shaft fractures, traumatic hip dislocations, femoral neck fractures, or tibial shaft fractures will be recruited over a period of 24–36 months. Hospitalization and treatment details (including materials and implants) will be captured in a cloud-based, searchable database. Outcome measures include radiographic assessments, clinical outcomes (such as range of motion, limb length discrepencies, and implant removal), patient-reported outcomes (PROOF™, PROMIS®, and EQ-5D-Y), and adverse events.

Aside from descriptive statistics on patient demographics, baseline characteristics, types of fractures, and adverse event rates, research questions will be formulated based on data availability and quality. A statistical analysis plan will be prepared before the statistical analysis.

Ethics and dissemination

Ethics approval will be obtained before patients are enrolled at each participating site. Patient enrollment will follow an informed consent process approved by the responsible ethics committee. Peer-reviewed publication is planned to disseminate the study results.

Registration

This study is registered under ClinicalTrials.gov: NCT04207892.

Keywords

Pediatric orthopedics, trauma management, patient reported outcome measures, registries, pediatric surgery

Strengths and limitations of this study

- The study will provide high-quality, prospective data on treatment details and outcomes from a large cohort of pediatric orthopedic traumas.
- The collection of a comprehensive, standardized set of data in a searchable database will facilitate future research in comparing the effectiveness and outcome of different treatments.
- Global participation is intended for this study which should ensure that results are broadly applicable and allow a comparison of regional practices.
- Conversely, global participation of study sites could mean a broad spectrum of treatment practices and variance in data quality. It is possible that such a large variation could impair data analysis.

INTRODUCTION

Caring for pediatric musculoskeletal injuries requires specialized knowledge and close monitoring. Because these patients, whether an infant, child, or adolescent, are still in the growth and development stage with open physes, dedicated effort and careful consideration of the needs of a growing child are necessary. In addition, the quality of care needs to be regularly evaluated against available benchmarks to promote continuous innovation and improvement to existing treatment modalities (1).

Currently, multiple pediatric fractures and musculoskeletal injuries with significant management controversy or clinical equipoise exist. These include fractures of the proximal humerus, distal humerus, proximal radius, forearm shaft, femoral neck, tibial shaft, and traumatic hip dislocations. Both nonoperative and operative treatments have been described in the literature for these injuries with no clear evidence or consensus on preferred treatment modalities. Nevertheless, recent research has demonstrated a trend towards operative treatments and promising results (2). The situation clearly demands better, high-quality clinical evidence.

The rarity of these injuries, however, presents a challenge. Few if any prospective studies with large sample sizes have been conducted and current literature on these injuries has been limited to case studies or retrospective studies of small sample sizes. Although patient data may be retrieved from hospital charting systems for evaluating different treatment modalities, they may not present a complete or accurate picture and therefore are limited in utility.

In our current study, we have designed a prospective, multicenter observational cohort study covering the above-mentioned injuries with management controversy or clinical equipoise. The study is dedicated to capturing treatment details and outcomes in a standardized and accessible format from a large cohort. It can therefore be a powerful tool for data mining to compare different treatment methods in real-world settings and promote evidence-based fracture care in pediatric patients in developing and developed countries. Because management strategies are likely to differ between low-, middle-, and high-income countries due to differences in resources and local context (3), participating sites from different geographical regions will be included to ensure that results may be broadly applicable. We believe that this prospective, multicenter study with a large cohort will be valuable in providing much needed high-quality evidence. Additionally, the injuries will be classified according to the AO Pediatric Comprehensive Classification of Long Bone Fractures (AO PCCF) (1); the results shall help validate the AO PCCF and determine its utility in treatment decision-making and predicting fracture outcomes.

METHODS AND ANALYSIS

Study design and setting

This is a prospective global multicenter observational cohort study serving the function of a pediatric orthopedic research, trauma, and health outcomes (PedORTHO) registry. Table 1 summarizes the sites that are currently included in the study; all are specialized pediatric fracture care centers.

Standardized data on fracture management and outcomes will be collected in a customized, searchable database. All treatments will be performed according to the usual practice at participating sites; no study-specific treatments, selection of materials, or surgical techniques are dictated in the study protocol, except for the prospective collection of a standardized set of data (demographic information, baseline injury information, diagnosis, treatment details,

and clinical and patient-reported outcomes). Posttreatment care and follow-up visits will also be conducted according to the standard procedures at participating sites.

Table 1: Current participating sites

Name	Country	Region
Tamale Teaching Hospital Trauma Orthopaedics Clinic, Tamale	Ghana	Africa
Lady Reading Hospital, Peshawar	Pakistan	Asia
Tejasvini Hospital & SSIOT, Mangalore	India	Asia
Queensland Children's Hospital, Brisbane	Australia	Australia
The Children's Hospital at Westmead, Sydney	Australia	Australia
Kinderchirurgische Klinik, Städtisches Klinikum Karlsruhe, Karlsruhe	Germany	Europe
Clinical Hospital Center Rijeka CHCR, Pediatric Surgery Clinic, Rijeka	Croatia	Europe
Karamandaneio Children's Hospital, Patras	Greece	Europe
Hospital Universitario del Rio Hortega, Valladolid	Spain	Europe
Hospital Sant Joan de Deu of Barcelona, Barcelona	Spain	Europe
BC Children's Hospital, Vancouver	Canada	North America
Children's Hospital of Eastern Ontario Research Institute, Ottawa	Canada	North America
University of Missouri Health Care Missouri Orthopaedic Institute, Columbia	Unites States	North America
The Hospital for Sick Children, Toronto	Canada	North America
Izaak Walton Killam (IWK) Health Centre, Halifax	Canada	North America
Hospital Universitario de Caracas, Caracas	Venezuela	South America
Instituto de Aparato Locomotor y de Rehabilitacion Facultad de Medicina, Universidad Austral de Chile, Valdivia	Chile	South America

Study procedures

In this study, fractures are classified according to the AO PCCF (1). Open growth plate is defined as radiologically confirmed open physis in the injured bone.

Inclusion criteria

Patients diagnosed with the following isolated long bone fractures or dislocation with open growth plates will be included:

- Proximal humerus fractures (AO PCCF 11-E/1.1; 11-E/4.1,4.2; 11-E/2.1,2.2; 11-E/8.1, 8.2; 11-E/3.1, 3.2 and 11-M/3.1,3.2)
- Distal humerus fractures (AO PCCF 13-M/3.1 III + IV; 13-M/3.2 III + IV; 13-E/1.1, 2.1, 3.1, 3.2, 4.1, 4.2 and 13-E/8.1, 8.2)
- Proximal radius fractures
- Forearm shaft fractures
- Femoral neck fractures
- Tibial shaft fractures (AO PCCF 42-D/4.1, 4.2, 5.1, 5.2 and 42t-D/4.1, 4.2, 5.1, 5.2, with or without fibula fracture)
- Traumatic hip dislocations (Steward & Milford Classification) (4)

Exclusion criteria

Patients with radiologically confirmed closed physis in the injured bones and/or diagnosed with the following fractures will be excluded:

- Supracondylar humerus fracture of AO PCCF 13-M/3.1 I; 13-M/3.1 II and 13-M/3.2 II
- Proximal humerus fracture of AO PCCF 11-M/2.1
- Tibia shaft fracture of AO PCCF 42-D/1.1, 2.1 and 42t-D/1.1, 2.1, 3.1, with or without fibula fracture

Patients with polytrauma or multiple fractures, previous fracture of the same anatomical region, other underlying musculoskeletal or neuromuscular disorder, or fractures 4 weeks old or older before treatment will also be excluded.

Recruitment

A recruitment period of 24–36 months is planned to enroll 750–1000 eligible patients. Patient enrollment will be consecutive with no limit in the number of patients enrolled at each site. However, a limit of 200 patients will be applied to each fracture type to ensure sufficient coverage of different types of fractures. Additionally, the numbers of enrollments are also limited for different fracture types at each site to ensure a reasonable distribution of different fracture types and the multicenter perspectives are maintained for each fracture type.

Potentially eligible patients are screened according to the inclusion and exclusion criteria. A member of the research team from the study site will explain the nature of the registry, its purpose, procedures involved, the expected duration, the potential risks and benefits, any discomfort it may entail, and the informed consent process to each patient and the parent(s) or legal guardian using lay language. Patients and parents (or legal guardians) will be informed that participation in the registry is voluntary and that they may withdraw at any time without affecting subsequent medical treatments. They will also be informed that the child's medical records may be examined by authorized individuals other than the treating physician. The patient information sheets provided to the children were adapted so that they are age appropriate, accompanied by an oral explanation. Because the patients are minors, the informed consent forms will be dated and signed by either the parents or legal guardians. Written assent may also be obtained from older children who can understand the information during the informed consent process.

In general, consent will be obtained before any treatments or assessments take place, but the latest at the first follow-up visit, i.e., Visit 3 (Table 2).

Data collection

A summary of data to be collected at each visit is illustrated in Table 2.

Table 2: Data collection at each visit

	Pre-, intra-, and postoperative visits [1]							
Assessment parameters	**Visit 1** Screening/ preoperative	**Visit 2** treatment (Day 0)	**Visit 3** 3-8 weeks	**Visit 4** 3 months (± 2weeks)	**Visit 5** 6 months (± 4 weeks)	**Visit 6** 12 months (± 4 weeks)	**Visit 7** 24 months (± 8 weeks)	**Additional visits[4]** According to standard of care
Eligibility	X							

Patient information/consent	X							
Demographics and baseline information	X							
Fracture and trauma details	X							
Treatment details		X						X
Radiographic outcomes			X	X	X	X	X	X
Clinical/functional outcomes[2]			X	X	X	X	X	X
Patient-reported outcomes[2]			X	X	X	X[3]	X[3]	X
Adverse events		X	X	X	X	X	X	X

[1] Timing of postoperative follow-ups are calculated from the day of treatment (Day 0).
[2] Final clinical/functional outcomes should always be assessed at the final visit in the hospital.
[3] If no on-site visits are scheduled at 12 and 24 months, patient-reported outcomes may be completed electronically, on paper, or through an interview (e.g., via telephone).
[4] Conducted as needed or according to the local standard.
Informed consent must be obtained the latest on Visit 3, if this was not obtained at Visit 1 or Visit 2

Baseline information

Baseline parameters to be recorded are sex, year of birth, height and weight, the location and activity that caused the injury. Fracture details to be recorded are the fracture classification according to the AO PCCF, side of the fracture, high- or low-energy trauma, and open or closed fracture (5-7).

Treatment details

For nonoperative treatments, details to be collected include if closed reduction was performed, hardware used for immobilization (e.g., types and materials of casts, slings, and splints), post-reduction radiographic control, and length of hospitalization.

For surgical treatments, details to be recorded are (as applicable) the surgical approach, duration of surgery, open or closed reduction, details of implants, details of external immobilization, post-reduction radiographic control, length of hospitalization, and details of physical therapy.

Depending on the location of the fracture, additional relevant details may also be recorded. For example, in case of an operative treatment of a forearm shaft fracture, whether an ulnar osteotomy for plastic deformity or a radial head reduction was performed will be recorded.

Documented visits

Visits are documented by the investigators according the standard of care in their centers. Any additional unscheduled visits, such as for a medical emergency, will be documented as additional visits.

Termination of participation

Participation in this registry may terminate early for reasons such as patient withdrawal of informed consent, investigator's discretion (e.g., patient noncompliance), loss to follow-up, death, and patient found to be ineligible.

Early terminations will be recorded in a dropout form, including the circumstances leading to the termination. All patient data collected prior to the termination will be censored as of the day of the official termination. No further data will be collected from these patients. Censored data will be included in the analyses, except when patients explicitly request their removal.

Outcome measures

Radiographic outcomes

Radiographs taken according to local standard of care are evaluated by the principal investigators at the study sites to assess fracture healing and alignment. Standardized radiographic measurements will be collected according to the image evaluation manual provided to each investigator site. These measurements are:

- Proximal humerus fractures: proximal humerus angulation
- Distal humerus fractures: Baumann angle, anterior humeral line (if it dissects the capitellum), and lateral capitello-humeral angle
- Proximal radius fractures: radial head angulation and carrying angle
- Forearm shaft fractures: radius and/or ulna, volar tilt (radius), and radial inclination
- Traumatic hip dislocations: acutely concentric reduction (yes/no), articulo-trochanteric distance, evidence of avascular necrosis (yes/no; if yes, Ratliff classification of avascular necrosis), evidence of heterotopic ossification (yes/no), evidence of premature physeal closure (yes/no), femoral neck length (compared to contralateral site, if radiograph is available through local standard of care)
- Femoral neck fractures: neck shaft angle, articulo-trochanteric distance, evidence of avascular necrosis (yes/no), Ratliff classification of avascular necrosis, evidence of premature physeal closure (yes/no), quality of reduction, femoral neck length (compared to contralateral site, if radiograph is available through local standard of care)
- Tibial shaft fractures: with or without fibula fracture, lateral distal tibial angle, medial proximal tibial angle, and tibial slope

Additional radiographic analyses may be performed at a later stage.

Clinical outcomes

Clinical outcomes to be assessed (Table 2) are:

- Malalignment (compared to the contralateral side) and impaired range of motion (abduction/adduction, supination/pronation, internal rotation/external rotation, and flexion/extension)
- Leg length discrepancy (LLD) measured according to the standing blocks method (8)
- Time (in weeks) to return to full activity, full weight-bearing, and return to kindergarten or school
- Implant removal (yes/no; if yes, whether planned). Unplanned implant removal will be documented as an adverse event (AE).

Patient-reported outcomes

Patient-reported outcomes (Table 2) to be assessed include the PROOF™ (Patient Reported Outcomes Of Fracture Healing) (9), PROMIS® (Patient-Reported Outcomes Measurement Information System®) (10), and EQ-5D-Y (11).

PROOF™ was developed for outcome evaluation of fracture treatments in children from the perspectives of both patients and their parents; it is currently being validated. The instrument

has 4 domains: how the limb looks, how the limb feels, how the limb works, and how it is healing (9). The last domain is assessed only at the final visit and includes: the length of hospitalization, number of visits to the doctor, number of AEs, perception of pain during the recovery period, time away from school, lost work, out of pocket expenses, and overall experience of the recovery. Standardized scores from 0 to 100 are reported for each of the four domains and as total scores. The instrument is only available in English. PROOF™ will not be administered in sites where English is not the native language, except when the parents or patients can understand English at a level that allows a clear and correct assessment.

PROMIS® offers a set of person-centered measures for assessing physical, mental, and social health in adults and children (10). For this registry, the PROMIS Physical Function (the Mobility short form) and the PROMIS Pain Interference instruments are used. The Mobility short form measures self-reported capability and not the actual performance, and the PROMIS Pain Interference assesses self-reported consequences of pain on aspects of one's life. Both are available for children 8 years and older and for parents (proxy administration) of children older than 5 years. Currently, these instruments are not available in local languages for all sites. For sites that the instrument is not available in local languages, these measurements will not be assessed, except when the parents or patients can understand English at a level that allows a clear and correct assessment.

The EQ-5D-Y is a child-friendly version of the EQ-5D developed based on the EQ-5D-3L (11). It is a self-filled questionnaire recommended in general for children and adolescents aged 8–15 years, in accordance with the user guide, we are using the EQ-5D-Y across the full age range of the study to avoid using two different versions of EQ-5D (12). For children aged 4–7 years, an EQ-5D-Y proxy version will be answered by a parent, caregiver, or health professional. The proxy will be asked to provide their own impression of the child or adolescent's health status on the day of administration.

Adverse events

Since this is a observational study, only AEs potentially related to the treatments, implant used, or the medical condition under investigation will be recorded. These include neurological injuries, vascular injuries, wound infections, wound healing problems, implant failure, loss of reduction that requires additional interventions, re-fractures, delayed bone union or nonunion, malalignment at final visits, persistent pain, limitation in motion, LLD >1.5cm, and other AEs that could influence the outcome of the treatment.

Statistical considerations

Sample size determination

The objectives of this study are descriptive and exploratory in nature without a formal hypothesis, therefore, a sample size calculation was not performed. The proposed number of patients to be included in this registry (750–1,000) was estimated to allow the identification of infrequent AEs and rare treatment concepts, and is deemed practically achievable over an enrollment period of 24–36 months.

Statistical analysis

A statistical analysis plan (SAP) will be prepared before any statistical analysis. In general, descriptive summary statistics will be generated for patient demographics, baseline characteristics, types of fractures, surgical and nonoperative treatment details, outcomes, and AEs. Categorical variables will be summarized using the frequency and percentage;

continuous variables will be summarized using mean, standard deviation, median, inter-quartile range, and minimum and maximum values. These summary statistics will also be presented according to clinically relevant categories such as treatment type and age.

AEs will be reported both at patient and event level. AE rates with 95% confidence intervals will be calculated based on the full analysis population, irrespective of dropouts.

Depending on the quality of the data and the number of patients in specific sub-populations (e.g., different age and treatment groups), research questions may be formulated and appropriate statistical analyses performed. Details concerning other analyses and the handling of missing data will be specified in the SAP.

Data collection and monitoring

Data from participating patients are documented in electronic case report forms (CRFs) and captured in the REDCap Cloud Electronic Data Capture system (https://www.redcapcloud.com/). CRFs are to be completed in a timely manner and are password protected—only authorized personnel have access. After termination of the registry, each site will receive an electronic copy of its own data.

Images collected in association with this study will be de-identified and sent to the sponsor digitally.

Due to the observational nature of the study, a data monitoring safety board has not been implemented. Regular data monitoring and cleaning will be performed to ensure data accuracy.

Current status

Currently, the participating sites include 17 centers from Africa, Asia, Australia, Europe, North America, and South America. All have obtained ethics approval and started enrolling patients.

DISCUSSION

In a 2008 policy statement, the American Academy of Pediatrics recognized the importance of comprehensive trauma registries in facilitating periodic patient care review, a key priority for patient safety and outcome improvement (13). Yet, prospective trauma registries in pediatric care are still rare today, especially in the area of fracture care. To prospectively collect a standardized set of data on pediatric orthopedic fracture care, we have embarked on setting up a global, multicenter pediatric registry to collect data on key long bone fractures and traumatic hip dislocation, their treatments, and health outcomes.

We expect this registry to provide a comprehensive set of data that allows retrospective comparative analyses on the effectiveness of different treatments. The results shall be high-quality real-world evidence that can fascilitate policy-making and help implement evidence-based protocols for standard care. This in turn, would improve quality of care, reduce patient morbidity and mortality (13), support efficient and effective patient follow-up leading to better resource allocation.

A registry of this scope and rigour that includes sites from around the world provides the potential for efficient publication of clinically relevant results and effective knowledge translation amongst the global pediatric orthopedic community. Unlike the traditional multicenter research that usually includes only patients in the Global North, this registry will include sites from regions such as Africa, Asia, and South America—regions that are usually underrepresented in clinical research. Therefore, the results from this registry should be

broadly generalizable to the global pediatric population. This is particularly important as the volume of traumatic injuries and the mechanisms of injury differ between low-, middle-, and high-income countries (3).

In summary, this protocol describes our approach to collect treatment and outcome data on key long bone fractures and traumatic hip dislocations in a pediatric population where substantial clinical equipoise or controversy exists. By broadly capturing the treatment details across centers and regions, this study should help identify treatments with superior outcomes and optimize the management of these injuries.

ETHICS AND DISSEMINATION

Ethics approval was obtained from the local ethics committee or institutional review board prior to patient enrollment. The registry has been designed and implemented according to current valid international standards (ICH GCP and ISO 14155) and based on the ethical position of the Declaration of Helsinki, to ensure optimal protection of patient interests. It is intended that the results of this study shall be published in peer-reviewed journals and presented at suitable conferences.

PATIENT AND PUBLICA INVOLVEMENT STATEMENT

This protocol was designed without patient and public involvement.

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AUTHORS CONTRIBUTIONS

E. S., K. M., and A. J. initiated and designed the study and contributed to the writing of the protocol and the manuscript. B.Z. and M.C. contributed to the writing of the protocol and the manuscript. All members of the PedORTHO Study Group contributed to the design of the study and critical reading and approving the protocol and manuscript. E. S. is the guarantor of this manuscript.

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COMPETING INTERESTS

None declared

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Bryn Zomar[1], Maio Chen[2], Emily Schaeffer[1], Kishore Mulpuri[1], PedORTHO Study Group, Alexander Joeris[2]

[1]: Department of Orthopaedics, The University of British Columbia; BC Children's Hospital, Vancouver, Canada

[2]: AO Foundation Innovation Translation Center, Davos, Switzerland

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Correspondence to Dr Emily Schaeffer; Emily.schaeffer@cw.bc.ca

ABSTRACT

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Management controversy and clinical equipoise exists in treatments of long bone fractures and traumatic hip dislocation in pediatric patients due to the lack of high-quality clinical evidence. This protocol describes the effort of a large prospective global multicenter cohort study (registry) aiming at providing quality data to assist evidence-based treatment decision-making.

Methods and analysis

Eligible pediatric patients (N=750–1000) with open physes suffering from proximal humerus fractures, distal humerus fractures, proximal radius fractures, forearm shaft fractures, traumatic hip dislocations, femoral neck fractures, or tibial shaft fractures will be recruited over a period of 24–36 months. Hospitalization and treatment details (including materials and implants) will be captured in a cloud-based, searchable database. Outcome measures include radiographic assessments, clinical outcomes (such as range of motion, limb length discrepencies, and implant removal), patient-reported outcomes (PROOF™, PROMIS®, and EQ-5D-Y), and adverse events.

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Keywords

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Strengths and limitations of this study

- The study will be conducted as a prospective global registry; it will collect high-quality, prospective data on treatment details and outcomes from a large cohort of pediatric orthopedic traumas.
- Collection of a comprehensive, standardized set of data in a searchable database will enable comparison of treatment effectiveness and outcomes.
- Global participation of study sites will ensure that results are broadly applicable, allow for comparison of regional practices, and enable the recruitment of a larger number of participants with rare injuries.
- Variance in data quality due to the global participation of study sites is a limitation of the study design.
- Another limitation is the collection of multiple patient-reported outcomes, which poses a burden to patients and may lead to missing information and reduced data quality.

INTRODUCTION

Caring for pediatric musculoskeletal injuries requires specialized knowledge and close monitoring. Because these patients, whether an infant, child, or adolescent, are still in the growth and development stage with open physes, dedicated effort and careful consideration of the needs of a growing child are necessary. In addition, the quality of care needs to be regularly evaluated against available benchmarks to promote continuous innovation and improvement to existing treatment modalities (1).

Currently, multiple pediatric fractures and musculoskeletal injuries with significant management controversy or clinical equipoise exist. These include fractures of the proximal humerus, distal humerus, proximal radius, forearm shaft, femoral neck, tibial shaft, and traumatic hip dislocations. For instance, there is little research comparing the effectiveness of surgical versus nonsurgical treatments for severely displaced proximal humerus fractures in pediatric populations, and most existing clinical studies enrolled only a small number of patients (2-7). Similarly, multiple authors have found no difference in the long-term functional outcomes between surgical and nonsurgical treatment in patients with moderately displaced medial epicondyle fractures. However, these studies lack standardized criteria on how displacements were measured and did not differentiate between sedentary and active pediatric populations (8, 9). Finally, limited evidence is currently available that compares different treatments and radiographic techniques for traumatic hip dislocations in pediatric patients. The rarity of this injury has restricted existing literature to case studies only (10). The situation for these injuries clearly demands better, high-quality clinical evidence.

The rarity of some of these injuries, however, presents a challenge. Few if any prospective studies with large sample sizes have been conducted and current literature on these injuries has been limited to case studies or retrospective studies of small sample sizes. Although patient data may be retrieved from hospital charting systems for evaluating different treatment modalities, they may not present a complete or accurate picture and therefore are limited in utility.

In our current study, we have designed a prospective, multicenter observational cohort study covering the above-mentioned injuries with management controversy or clinical equipoise. The study is dedicated to capturing treatment details and outcomes in a standardized and accessible format from a large cohort. It can therefore be a powerful tool for data mining to compare different treatment methods in real-world settings and promote evidence-based fracture care in pediatric patients in developing and developed countries. Because management strategies are likely to differ between low-, middle-, and high-income countries due to differences in resources and local context (11), participating sites from different geographical regions will be included to ensure that results may be broadly applicable. We believe that this prospective, multicenter study with a large cohort will be valuable in providing much needed high-quality evidence. Additionally, the injuries will be classified according to the AO Pediatric Comprehensive Classification of Long Bone Fractures (AO PCCF) (1); the results shall help validate the AO PCCF and determine its utility in treatment decision-making and predicting fracture outcomes.

METHODS AND ANALYSIS

Study design and setting

This is a prospective global multicenter observational cohort study serving the function of a pediatric orthopedic research, trauma, and health outcomes (PedORTHO) registry. Table 1 summarizes the sites that are currently included in the study; all are specialized pediatric fracture care centers.

Standardized data on fracture management and outcomes will be collected in a customized, searchable database. All treatments will be performed according to the usual practice at participating sites; no study-specific treatments, selection of materials, or surgical techniques are dictated in the study protocol, except for the prospective collection of a standardized set of data (demographic information, baseline injury information, diagnosis, treatment details, and clinical and patient-reported outcomes). Posttreatment care and follow-up visits will also be conducted according to the standard procedures at participating sites.

Table 1: Current participating sites

Name	Country	Region
Tamale Teaching Hospital Trauma Orthopaedics Clinic, Tamale	Ghana	Africa
Lady Reading Hospital, Peshawar	Pakistan	Asia
Tejasvini Hospital & SSIOT, Mangalore	India	Asia
Queensland Children's Hospital, Brisbane	Australia	Australia
The Children's Hospital at Westmead, Sydney	Australia	Australia
Kinderchirurgische Klinik, Städtisches Klinikum Karlsruhe, Karlsruhe	Germany	Europe
Clinical Hospital Center Rijeka CHCR, Pediatric Surgery Clinic, Rijeka	Croatia	Europe
Karamandaneio Children's Hospital, Patras	Greece	Europe
Hospital Universitario del Rio Hortega, Valladolid	Spain	Europe
Hospital Sant Joan de Deu of Barcelona, Barcelona	Spain	Europe
BC Children's Hospital, Vancouver	Canada	North America
Children's Hospital of Eastern Ontario Research Institute, Ottawa	Canada	North America
University of Missouri Health Care Missouri Orthopaedic Institute, Columbia	Unites States	North America
The Hospital for Sick Children, Toronto	Canada	North America
Izaak Walton Killam (IWK) Health Centre, Halifax	Canada	North America
Hospital Universitario de Caracas, Caracas	Venezuela	South America
Instituto de Aparato Locomotor y de Rehabilitacion Facultad de Medicina, Universidad Austral de Chile, Valdivia	Chile	South America

Study procedures

In this study, fractures are classified according to the AO PCCF (1). Open growth plate is defined as radiologically confirmed open physis in the injured bone. Inclusion criteria were determined according to the existence of substantial clinical equipoise or management controversy for specific fractures. To reduce confounding factors, we opted to exclude patients with multiple injuries. Additionally, femoral shaft fractures are not included as we are currently conducting a separate study focused on these fractures.

Inclusion criteria

Patients diagnosed with the following isolated long bone fractures or dislocation with open growth plates will be included:

- Proximal humerus fractures (AO PCCF 11-E/1.1; 11-E/4.1,4.2; 11-E/2.1,2.2; 11-E/8.1, 8.2; 11-E/3.1, 3.2 and 11-M/3.1,3.2)
- Distal humerus fractures (AO PCCF 13-M/3.1 III + IV; 13-M/3.2 III + IV; 13-E/1.1, 2.1, 3.1, 3.2, 4.1, 4.2 and 13-E/8.1, 8.2)
- Proximal radius fractures

- Forearm shaft fractures
- Femoral neck fractures
- Tibial shaft fractures (AO PCCF 42-D/4.1, 4.2, 5.1, 5.2 and 42t-D/4.1, 4.2, 5.1, 5.2, with or without fibula fracture)
- Traumatic hip dislocations (Steward & Milford Classification) (12)

Exclusion criteria

Patients with radiologically confirmed closed physis in the injured bones and/or diagnosed with the following fractures will be excluded:

- Supracondylar humerus fracture of AO PCCF 13-M/3.1 I; 13-M/3.1 II and 13-M/3.2 II
- Proximal humerus fracture of AO PCCF 11-M/2.1
- Tibia shaft fracture of AO PCCF 42-D/1.1, 2.1 and 42t-D/1.1, 2.1, 3.1, with or without fibula fracture

Patients with polytrauma or multiple fractures, previous fracture of the same anatomical region, other underlying musculoskeletal or neuromuscular disorder, or fractures 4 weeks old or older before treatment will also be excluded.

Recruitment

A recruitment period of 24–36 months is planned to enroll 750–1000 eligible patients. Patient enrollment will be consecutive with no limit in the number of patients enrolled at each site. However, a limit of 200 patients will be applied to each fracture type to ensure sufficient coverage of different types of fractures. Additionally, the numbers of enrollments are also limited for different fracture types at each site to ensure a reasonable distribution of different fracture types and the multicenter perspectives are maintained for each fracture type.

Potentially eligible patients are screened according to the inclusion and exclusion criteria. A member of the research team from the study site will explain the nature of the registry, its purpose, procedures involved, the expected duration, the potential risks and benefits, any discomfort it may entail, and the informed consent process to each patient and the parent(s) or legal guardian using lay language. Patients and parents (or legal guardians) will be informed that participation in the registry is voluntary and that they may withdraw at any time without affecting subsequent medical treatments. They will also be informed that the child's medical records may be examined by authorized individuals other than the treating physician. The patient information sheets provided to the children were adapted so that they are age appropriate, accompanied by an oral explanation. Because the patients are minors, the informed consent forms will be dated and signed by either the parents or legal guardians. Written assent may also be obtained from older children who can understand the information during the informed consent process.

In general, consent will be obtained before any treatments or assessments take place, but the latest at the first follow-up visit, i.e., Visit 3 (Table 2).

Data collection

A summary of data to be collected at each visit is illustrated in Table 2. For patients with no on-site visits scheduled, patient-reported outcomes may be completed electronically, on paper, or through telephone interviews.

Table 2: Data collection at each visit

Assessment parameters	Pre-, intra-, and postoperative visits [1]							
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Additional Visits[3]
	Screening/ preoperative	treatment (Day 0)	3-8 weeks	3 months (± 2weeks)	6 months (± 4 weeks)	12 months (± 4 weeks)	24 months (± 8 weeks)	According to standard of care
Eligibility	X							
Patient information/consent	X							
Demographics and baseline information	X							
Fracture and trauma details	X							
Treatment details		X						X
Radiographic outcomes			X	X	X	X	X	X
Clinical/functional outcomes[2]			X	X	X	X	X	X
Patient-reported outcomes[2]			X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X

[1] Timing of postoperative follow-ups are calculated from the day of treatment (Day 0).
[2] Final clinical/functional outcomes should always be assessed at the final visit in the hospital.
[3] Conducted as needed or according to the local standard.
Informed consent must be obtained the latest on Visit 3, if this was not obtained at Visit 1 or Visit 2

Baseline information

Baseline parameters to be recorded are sex, year of birth, height and weight, the location and activity that caused the injury. Fracture details to be recorded are the fracture classification according to the AO PCCF, side of the fracture, high- or low-energy trauma, and open or closed fracture (13-15).

Treatment details

For nonoperative treatments, details to be collected include if closed reduction was performed, hardware used for immobilization (e.g., types and materials of casts, slings, and splints), post-reduction radiographic control, and length of hospitalization.

For surgical treatments, details to be recorded are (as applicable) the surgical approach, duration of surgery, open or closed reduction, details of implants, details of external immobilization, post-reduction radiographic control, length of hospitalization, and details of physical therapy.

Depending on the location of the fracture, additional relevant details may also be recorded. For example, in case of an operative treatment of a forearm shaft fracture, whether an ulnar osteotomy for plastic deformity or a radial head reduction was performed will be recorded.

Documented visits

Visits are documented by the investigators according the standard of care in their centers. Any additional unscheduled visits, such as for a medical emergency, will be documented as additional visits.

Termination of participation

Participation in this registry may terminate early for reasons such as patient withdrawal of informed consent, investigator's discretion (e.g., patient noncompliance), loss to follow-up, death, and patient found to be ineligible.

Early terminations will be recorded in a dropout form, including the circumstances leading to the termination. All patient data collected prior to the termination will be censored as of the day of the official termination. No further data will be collected from these patients. Censored data will be included in the analyses, except when patients explicitly request their removal.

Outcome measures

Radiographic outcomes

Radiographs taken according to local standard of care are evaluated by the principal investigators at the study sites to assess fracture healing and alignment. Standardized radiographic measurements will be collected according to the image evaluation manual provided to each investigator site. These measurements are:

- Proximal humerus fractures: proximal humerus angulation
- Distal humerus fractures: Baumann angle, anterior humeral line (if it dissects the capitellum), and lateral capitello-humeral angle
- Proximal radius fractures: radial head angulation and carrying angle
- Forearm shaft fractures: radius and/or ulna, volar tilt (radius), and radial inclination
- Traumatic hip dislocations: acutely concentric reduction (yes/no), articulo-trochanteric distance, evidence of avascular necrosis (yes/no; if yes, Ratliff classification of avascular necrosis), evidence of heterotopic ossification (yes/no), evidence of premature physeal closure (yes/no), femoral neck length (compared to contralateral site, if radiograph is available through local standard of care)
- Femoral neck fractures: neck shaft angle, articulo-trochanteric distance, evidence of avascular necrosis (yes/no), Ratliff classification of avascular necrosis, evidence of premature physeal closure (yes/no), quality of reduction, femoral neck length (compared to contralateral site, if radiograph is available through local standard of care)
- Tibial shaft fractures: with or without fibula fracture, lateral distal tibial angle, medial proximal tibial angle, and tibial slope

Additional radiographic analyses may be performed at a later stage.

Clinical outcomes

Clinical outcomes to be assessed (Table 2) are:

- Malalignment (compared to the contralateral side) and impaired range of motion (abduction/adduction, supination/pronation, internal rotation/external rotation, and flexion/extension)
- Leg length discrepancy (LLD) measured according to the standing blocks method (16)
- Time (in weeks) to return to full activity, full weight-bearing, and return to kindergarten or school
- Implant removal (yes/no; if yes, whether planned). Unplanned implant removal will be documented as an adverse event (AE).

Patient-reported outcomes

Patient-reported outcomes (Table 2) to be assessed include the PROOF™ (Patient Reported Outcomes Of Fracture Healing) (17), PROMIS® (Patient-Reported Outcomes Measurement Information System®) (18), and EQ-5D-Y (19).

PROOF™ was developed for outcome evaluation of fracture treatments in children from the perspectives of both patients and their parents; it is currently being validated. The instrument has 4 domains: how the limb looks, how the limb feels, how the limb works, and how it is healing (17). The last domain is assessed only at the final visit and includes: the length of hospitalization, number of visits to the doctor, number of AEs, perception of pain during the recovery period, time away from school, lost work, out of pocket expenses, and overall experience of the recovery. Standardized scores from 0 to 100 are reported for each of the four domains and as total scores. The instrument is only available in English. PROOF™ will not be administered in sites where English is not the native language, except when the parents or patients can understand English at a level that allows a clear and correct assessment.

PROMIS® offers a set of person-centered measures for assessing physical, mental, and social health in adults and children (18). For this registry, the PROMIS Physical Function (the Mobility short form) and the PROMIS Pain Interference instruments are used. The Mobility short form measures self-reported capability and not the actual performance, and the PROMIS Pain Interference assesses self-reported consequences of pain on aspects of one's life. Both are available for children 8 years and older and for parents (proxy administration) of children older than 5 years. Currently, these instruments are not available in local languages for all sites. For sites that the instrument is not available in local languages, these measurements will not be assessed, except when the parents or patients can understand English at a level that allows a clear and correct assessment.

The EQ-5D-Y is a child-friendly version of the EQ-5D developed based on the EQ-5D-3L (19). It is a self-filled questionnaire recommended in general for children and adolescents aged 8–15 years, in accordance with the user guide, we are using the EQ-5D-Y across the full age range of the study to avoid using two different versions of EQ-5D (20). For children aged 4–7 years, an EQ-5D-Y proxy version will be answered by a parent, caregiver, or health professional. The proxy will be asked to provide their own impression of the child or adolescent's health status on the day of administration.

Adverse events

Since this is a observational study, only AEs potentially related to the treatments, implant used, or the medical condition under investigation will be recorded. These include neurological injuries, vascular injuries, wound infections, wound healing problems, implant failure, loss of reduction that requires additional interventions, re-fractures, delayed bone

union or nonunion, malalignment at final visits, persistent pain, limitation in motion, LLD >1.5cm, and other AEs that could influence the outcome of the treatment.

Statistical considerations

Sample size determination

The objectives of this study are descriptive and exploratory in nature without a formal hypothesis, therefore, a sample size calculation was not performed. The proposed number of patients to be included in this registry (750–1,000) was estimated to allow the identification of infrequent AEs and rare treatment concepts, and is deemed practically achievable over an enrollment period of 24–36 months.

Statistical analysis

A statistical analysis plan (SAP) will be prepared before any statistical analysis. In general, descriptive summary statistics will be generated for patient demographics, baseline characteristics, types of fractures, surgical and nonoperative treatment details, outcomes, and AEs. Categorical variables will be summarized using the frequency and percentage; continuous variables will be summarized using mean, standard deviation, median, inter-quartile range, and minimum and maximum values. These summary statistics will also be presented according to clinically relevant categories such as treatment type and age.

AEs will be reported both at patient and event level. AE rates with 95% confidence intervals will be calculated based on the full analysis population, irrespective of dropouts.

Depending on the quality of the data and the number of patients in specific sub-populations (e.g., different age and treatment groups), research questions may be formulated and appropriate statistical analyses performed. Details concerning other analyses and the handling of missing data will be specified in the SAP.

Data collection and monitoring

Data from participating patients are documented in electronic case report forms (CRFs) and captured in the REDCap Cloud Electronic Data Capture system (https://www.redcapcloud.com/). CRFs are to be completed in a timely manner and are password protected—only authorized personnel have access. After termination of the registry, each site will receive an electronic copy of its own data.

Images collected in association with this study will be de-identified and sent to the sponsor digitally.

Due to the observational nature of the study, a data monitoring safety board has not been implemented. Regular data monitoring and cleaning will be performed to ensure data accuracy.

Current status

Currently, the participating sites include 17 centers from Africa, Asia, Australia, Europe, North America, and South America. All have obtained ethics approval and started enrolling patients. The first patient was enrolled in June 2021, and the last visit for the last patient is expected in April 2027. The enrollment start date for each site is provided in Supplementary Table 1.

DISCUSSION

In a 2008 policy statement, the American Academy of Pediatrics recognized the importance of comprehensive trauma registries in facilitating periodic patient care review, a key priority for patient safety and outcome improvement (21). Yet, prospective trauma registries in pediatric care are still rare today, especially in the area of fracture care. To prospectively collect a standardized set of data on pediatric orthopedic fracture care, we have embarked on setting up a global, multicenter pediatric registry to collect data on key long bone fractures and traumatic hip dislocation, their treatments, and health outcomes.

We expect this registry to provide a comprehensive set of data that allows retrospective comparative analyses on the effectiveness of different treatments. The results shall be high-quality real-world evidence that can fascilitate policy-making and help implement evidence-based protocols for standard care. This in turn, would improve quality of care, reduce patient morbidity and mortality (21), support efficient and effective patient follow-up leading to better resource allocation.

A registry of this scope and rigour that includes sites from around the world provides the potential for efficient publication of clinically relevant results and effective knowledge translation amongst the global pediatric orthopedic community. Unlike the traditional multicenter research that usually includes only patients in the Global North, this registry will include sites from regions such as Africa, Asia, and South America—regions that are usually underrepresented in clinical research. Therefore, the results from this registry should be broadly generalizable to the global pediatric population. This is particularly important as the volume of traumatic injuries and the mechanisms of injury differ between low-, middle-, and high-income countries (11).

There are several limitations to our study. Firstly, we are sure to recruit greater numbers of patients with the more common injuries (such as elbow and forearm fractures), than those with more rare injuries (such as hip fractures and dislocations). Previous research has been limited by small numbers of patients for these rare injuries and we are sure to encounter similar challenges. However, given the multi-centered nature of the study, it most likely represents the best chance to overcome these problems. Additionally, like all registries, we are likely to have some amount of missing data, particularly for patient-reported outcomes, as all visits for the registry are part of standard of care and participants will likely be discharged from care with their treating clinician prior to our furthest time points. To address this, we have allowed for questionnaires to be collected electronically or via telephone interview so that participants who do not return to clinic, may still have complete data. Our protocol also suffers from a lack of patient involvement in its development. Due to this, it's possible that our study is missing the collection of outcomes that are important to patients and their families. However, as a registry study, it is a starting point to collect a database of pediatric fracture data. In future, patients can and should be involved in developing research questions and protocols for studies attempting to answer questions arising from the registry data. In addition, while the involvement of multiple centers from across the globe is a strength of the study, as it will allow for the generalizability of study results to the population as a whole, this also introduces variability in the data. The demographic and injury information is likely different from site to site, making direct comparisons between sites difficult. There is also the risk that data quality may suffer if some involved sites have fewer research resources than others. Data quality, however, will be monitored throughout the study and critical problems will be identified and addressed as soon as possible.

In summary, this protocol describes our approach to collect treatment and outcome data on key long bone fractures and traumatic hip dislocations in a pediatric population where substantial clinical equipoise or controversy exists. By broadly capturing the treatment details

across centers and regions, this study should help identify treatments with superior outcomes and optimize the management of these injuries.

ETHICS AND DISSEMINATION

Ethics approval was obtained from the local ethics committee or institutional review board prior to patient enrollment. Patient enrollment will follow an informed consent process approved by the responsible ethics committee. The list of the ethics committees involved in the study can be found in Supplementary Table 1. The registry has been designed and implemented according to current valid international standards (ICH GCP and ISO 14155) and based on the ethical position of the Declaration of Helsinki, to ensure optimal protection of patient interests. It is intended that the results of this study shall be published in peer-reviewed journals and presented at suitable conferences.

PATIENT AND PUBLICA INVOLVEMENT STATEMENT

This protocol was designed without patient and public involvement.

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AUTHORS CONTRIBUTIONS

E. S., K. M., and A. J. initiated and designed the study and contributed to the writing of the protocol and the manuscript. B.Z. and M.C. contributed to the writing of the protocol and the manuscript. All members of the PedORTHO Study Group contributed to the design of the study and critical reading and approving the protocol and manuscript. E. S. is the guarantor of this manuscript.

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COMPETING INTERESTS

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COLLABORATORS

PedORTHO Study Group: on behalf of the PedORTHO Study group: A D B Buunaaim, S Imran Buckari, M Ajith Kumar, L Johnson, D Little, P Schmittenbecher, A Bosak Versic, A Konstantopoulou, I Aguado Maestro, M Stitzman Wengrowicz, K Mulpuri, S Carsen, S K Gupta, U Narayanan, R El Hawary, M J Malaret Baldo, M Sepulveda. The paediatric departments of the following hospitals have initiated the PedORTHO project and will contribute by recruiting participants: University for Development Studies School of Medicine, Department of Surgery Tamale Teaching Hospital Trauma Orthopaedics Clinic, Tamale, Ghana; Orthopedics, Lady Reading Hospital, Peshawar, Pakistan; Department of Orthopaedic surgery, Tejasvini Hospital & SSIOT, Mangalore, India; Department of Orthopaedics, Children's Health Queensland Hospital and Health Service, Brisbane, Queensland, Australia; The Children's Hospital at Westmead, University of Sydney, Sidney, Australia; Kinderchirurgische Klinik, Klinikum Karlsruhe, Karlsruhe, Germany; Department od Pediatric Surgery Clinical Hospital Centre Rijeka, Rijeka, Croatia; Karamandaneio Children's Hospital, Patras, Greece; Department of orthopaedic Surgery,Hospital Universitario del Rio Hortega, Valladolid, Spain; Hospital Sant Joan de Deu, Barcelona, Spain; BC Children's Hospital, Vancouver, Canada; Children's Hospital of Eastern Ontario (CHEO) Research Institute, University of Ottawa, Ottawa, Canada; University of Missouri, Columbia, MO, United States; Division of Orthopaedic Surgery, University of Toronto, The Hospital for Sick Children, Toronto, Canada; Izaak Walton Killam (IWK) Health Centre, Halifax, NS, Canada; Hospital Universitario de Caracas, Caracas, Distrito Capital, Venezuela; Hospital Base Valdivia, Universidad Austral de Chile, Valdivia, Chile.

Supplementary Table 1

Center	EC/IRB	EC/IRB approval date	Enrollment starting date
Tamale Teaching Hospital Trauma Orthopaedics Clinic, Tamale, Ghana	Tamale Teaching Hospital Ethical Review Committee	22-Sep-21	03-Feb-23
Lady Reading Hospital, Peshawar, Pakistan	Lady Reading Hospital Medical Teaching Institution Ethical Review Board	25-Feb-21	07-Sep-22
Tejasvini Hospital & SSIOT, Mangalore, India	Tejasvini Hospital & SSIOT Ethical Committee	22-Jul-21	27-Nov-22
Queensland Children's Hospital, Brisbane, Australia	Children's Health Queensland Hospital and Health Service Human Research Ethics Committee	21-Jun-21	25-May-22
The Children's Hospital at Westmead, Sydney, Australia	Children's Health Queensland Hospital and Health Service Human Research Ethics Committee	21-Jun-21	21-Oct-22
Kinderchirurgische Klinik, Städtisches Klinikum Karlsruhe, Karlsruhe, Germany	Städtisches Klinikum Karlsruhe Kinderchirurgische Klinik Ethik Kommission	16-Nov-21	02-Aug-22
Clinical Hospital Center Rijeka CHCR, Pediatric Surgery Clinic, Rijeka, Croatia	University Hospital Centre Rijeka Ethics Committee	02-Dec-21	23-Mar-23
Karamandaneio Children's Hospital, Patras, Greece	"Karamandeio" General Children's Hospital of Patras Scientific Council	07-Jul-21	13-Mar-23
Hospital Universitario del Rio Hortega, Valladolid, Spain		05-Jul-21	27-Dec-22
Hospital Sant Joan de Deu of Barcelona, Barcelona, Spain	CEIm Fundació Sant Joan de Déu	27-May-21	05-Mar-23
BC Children's Hospital, Vancouver, Canada	UBC C&W Research Ethics Board	08-Oct-21	26-May-22
Children's Hospital of Eastern Ontario Research Institute, Ottawa, Canada	CHEO Research Ethics Board	27-Jan-21	10-Apr-22
University of Missouri Health Care Missouri Orthopaedic Institute, Columbia, United States	Institutional Review Board University of Missouri-Columbia	01-Mar-21	30-Jul-22
The Hospital for Sick Children, Toronto, Canada	SickKids REB	28-Oct-22	07-Feb-23
Izaak Walton Killam (IWK) Health Centre, Halifax, Canada	IWK Research Ethics	08-Jul-22	26-Jun-23
Hospital Universitario de Caracas, Caracas, Venezuela	Instituto Autónomo Hospital Universitario de Caracas Comité de Bioética	12-May-21	29-Jun-22
Instituto de Aparato Locomotor y de Rehabilitacion Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile	Comité Ético Científico mServicio de Salud Valdivia	12-Feb-21	13-Apr-22

Supplementary Table 1: List of the local ethics committees and institutional review boards that have approved the study, EC/IRB approval date and enrollment starting date.
Abbreviations: EC: Ethics Committee; IRB: Institutional Review Board.