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Epidemiology, aetiology, interventions and genomics in children with arthrogryposis multiplex congenita: protocol for a multisite registry

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ABSTRACT

Introduction Arthrogryposis multiplex congenita (AMC) is an umbrella term including hundreds of conditions with the common clinical manifestation of multiple congenital contractures. AMC affects 1 in 3000 live births and is caused by lack of movement in utero. To understand the long-term needs of individuals diagnosed with a rare condition, it is essential to know the prevalence, aetiology and functional outcomes in a large sample. The development and implementation of a multicentre registry is critical to gather this data. This registry aims to improve health through genetic and outcomes research, and ultimately identify new therapeutic targets and diagnostics for treating children with AMC.

Methods and analysis Participants for the AMC registry will be recruited from seven orthopaedic hospitals in North America. Enrollment occurs in two phases; Part 1 focuses on epidemiology, aetiology and interventions. For this part, retrospective and cross-sectional data will be collected using a combination of patient-reported outcomes and clinical measures. Part 2 focuses on core subset of the study team, including a geneticist and bioinformatician, identifying causative genes and linking the phenotype to genotype via whole genome sequencing to identify genetic variants and correlating these findings with pedigree, photographs and clinical information. Descriptive analyses on the sample of 400 participants and logistic regression models to evaluate relationships between outcomes will be conducted.

Ethics and dissemination Ethical approval has been granted from corresponding governing bodies in North America. Dissemination of findings will occur via traditional platforms (conferences, manuscripts) for the scientific community. Other modalities will be employed to ensure that all stakeholders, including youth, families and patient support groups, may be provided with findings derived from the registry. Ensuring the findings are circulated to a maximum amount of interested parties will ensure that the registry can continue to serve as a platform for hypothesis-driven research and further advancement for AMC.

STRENGTHS AND LIMITATIONS OF THIS STUDY:

⇒ A multisite registry for children with arthrogryposis provides a platform for hypothesis-driven research.
⇒ Collecting standardised and non-standardised patient-reported and caregiver-reported questionnaires and interviews, medical charts and photographs yields a rich dataset to describe the phenotype, patient outcomes and risk factors in arthrogryposis.
⇒ Whole genome sequencing can maximise the diagnostic yield of molecular diagnosis in this heterogeneous group of children.
⇒ The use of a longitudinal design in the future to describe the natural history will guide treatment planning, prognosis and provide education to youth and families.
⇒ Currently recruiting in specific orthopaedic hospitals in North America.

INTRODUCTION

Arthrogryposis or arthrogryposis multiplex congenita (AMC) is a term that describes a group of congenital conditions characterised by non-progressive joint contractures involving two or more body areas.[1] The primary underlying cause of AMC is suspected to be decreased fetal movement during development (ie, fetal akinesia), attributed to genetic and/or environmental factors.[2] Treatment currently consists of early intensive interventions that include stretching, casting and bracing to promote joint mobility and movement.[3–5] Whereas several chart reviews have documented outcomes after surgical correction,[6–8] designs are retrospective and preclude the selection of the best outcomes. Multisite studies are required to increase case numbers for more statistical power for epidemiological and genetic studies, particularly as AMC and associated diagnoses are rare. In addition, a prospective design provides the opportunity to use selected outcome

measures to describe the phenotype and function of children across diagnostic groups, guide intervention and prognosis.

To better understand the long-term needs of individuals diagnosed with a rare condition and to contribute to better health outcomes for these individuals, it is essential to know the frequency, specific diagnoses with their mechanisms and natural history.[9 10] In many cases, a specific molecular diagnosis remains elusive, despite the identification of numerous causative and candidate genes. Advances in molecular methods, such as whole exome or whole genome sequencing (WGS) have been useful in delineating novel gene mutations, locus heterogeneity and phenotype–genotype correlations.[2 10]

Several classification systems for AMC exist[11] according to clinical features including but not limited to the presence or absence of central nervous system involvement, genetic causes and aetiology. The classification by Bamshad and colleagues[12] divides individuals with multiple congenital contractures into amyoplasia, distal arthrogryposis (DA) and those with central nervous system involvement. DA can be further subdivided into 10 subtypes with autosomal dominant genetic mutations, while the syndromic cases may have central nervous system or neuromuscular origins.[12 13] Recent meta-analysis of reported genetic mutations showed potential involvement of over 400 genes in 29 groups based on biological process with considerable variability in phenotypic expression.[11] An understanding of the genetic pathways and their correlation to established AMC phenotypes and clinical classifications is essential for early diagnosis, prognosis and more effective, personalised therapies.

To address the knowledge gap in AMC, a paediatric registry was piloted in 2018[14] with 40 families at two Shriners Hospitals for Children sites in Montreal, Canada and Philadelphia, Pennsylvania, USA.[15] Variables included demographics for child and biological parents, newborn variables (eg, birth weight, gestations, interventions at birth, phenotype), parental lifestyle factors and medical history. The methods used for data collection were telephone interview with the primary caregiver and medical chart review[15] and findings indicated that genetic testing, including cytogenic (ie, karyotype, microarray) and molecular (ie, single gene, whole-exome/genome sequencing) was performed on 48% of the children, yet findings were negative or inconclusive in most.[15] Pursuing more advanced genetic testing has the potential to increase the yield of informative molecular diagnoses.[10 16 17] This pilot registry provided the opportunity to refine the preliminary data sets prior to implementation.[15] The aim of this current study is to expand the pilot protocol to a full-scale multisite registry[14 15] and correlate the phenotype to genotype in a large cohort of children with multiple congenital contractures.

Specifically, this multicentre registry will:

1. Determine the epidemiology of AMC, including the frequency, associated risk factors and healthcare utilisation.
2. Report on the functional outcomes and interventions of children across phenotypes.
3. Describe the genotype leading to a more thorough understanding of the pathways that lead to multiple congenital contractures, and illuminate the circumstances underlying the heterogeneity of phenotypic presentation.

Our overarching hypothesis is that identifying and understanding associated risk factors will guide prevention and/or prenatal detection for early intervention and better health outcomes; and identifying and understanding genetic mechanisms will lead to the development of a comprehensive classification system and contribute to personalised therapies, thus improving the overall health of children with AMC and their families (figure 1). The purpose of this manuscript is to detail the protocol development and implementation for a multisite AMC paediatric registry.

METHODS AND ANALYSIS

Study design

The proposed study will consist of a registry using both retrospective and cross-sectional data. Clinicians and researchers who identified gaps in research and clinical therapies for children presenting with AMC initiated this registry. Additionally, patient representation was ensured through exchanges with youth and family representatives to inform the choice of outcomes that are meaningful.

Patient and public involvement

Patient representation was ensured through exchanges via focus groups with youth and family representatives in order to inform the choice of outcomes that are meaningful to this group of stakeholders. Results of the pilot study will be disseminated to study participants via infographics and other knowledge translation media, and through national AMC support groups, websites and social media (eg, AMCSI).

Study setting

As the AMC registry is an evolving project, the addition of sites is ongoing. The AMC registry was initiated in 2019 at four Shriners Hospitals for Children in Montreal, Canada; Philadelphia, Pennsylvania, USA; Portland, Oregon, USA and Sacramento, California, USA. Three additional study sites in Chicago, Illinois, USA; Honolulu, Hawaii, USA and Greenville, South Carolina, USA were added in 2021. These sites were selected as they have the largest AMC patient pool across the Shriners network. Participating sites for the time being are exclusively within the Shriners network as funding was provided through this agency (clinical multisite grant #79150).

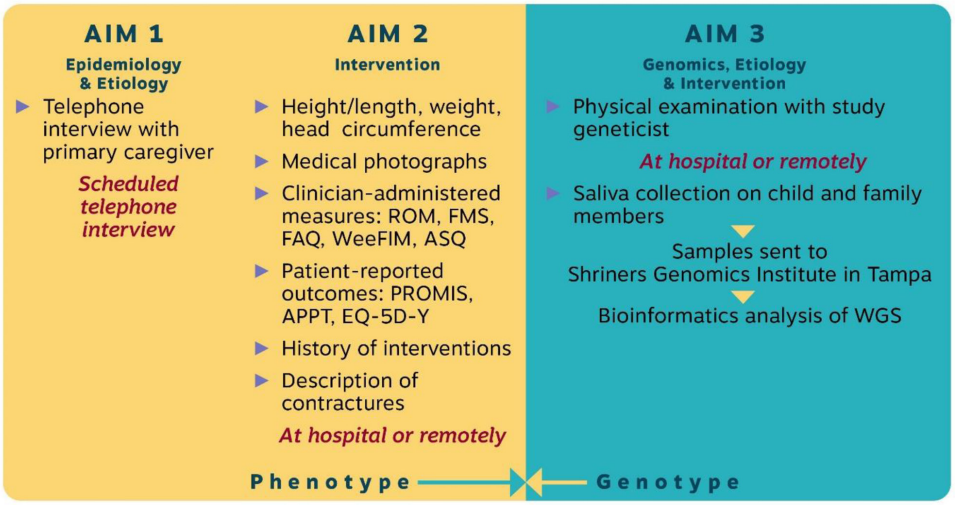

Figure 1 Data collected towards the correlation of the phenotype to the genotype. APPT, Adolescent and Pediatric Pain Tool; ASQ, Ages & Stages Questionnaire; EQ-5D-Y, EuroQOL-5D-Youth; FAQ, Gillette Functional Assessment Questionnaire; FMS, Functional Mobility Scale; PROMIS, Patient-Reported Outcomes Measurement Information System; ROM, range of motion; WeeFIM, The Functional Independence Measure for Children; WGS, whole genome sequencing.

Eligibility criteria, sample size and recruitment procedures

Families will be recruited based on having at least one child (0–21 years old) with the clinical manifestation of multiple congenital contractures in at least two different body areas as per the definition of AMC.[1] Eligibility will be confirmed using the electronic medical record and the input from the treating orthopaedic surgeon at each site. Those who do not provide signed informed consent, do not speak French, English or Spanish will be excluded. The recruitment plan includes face-to-face as well as remote accrual. Participants will be recruited during their hospital visit at each respective site by the local clinical research coordinator (CRC), who will provide information regarding the registry and review the consent/assent forms as appropriate. In the event there are no upcoming hospital visits scheduled in the next several months, the CRC may contact potential participants remotely by telephone to introduce the study. Once eligible participants provide verbal consent to participate, the CRC either will collect data face-to-face or remotely.

A tentative appointment for the telephone interview will be scheduled. However, if preferred by the family, they will be re-contacted by email to schedule an appointment. Based on the total patient population at each site, the overall recruitment target of 400 participants is set. The primary caregiver for each of the 400 families will complete the telephone interview with the CRC.

Data collection procedures

Epidemiology, aetiology and interventions

In order to gain insight into the natural history of AMC, several types of data will be collected through clinician-administered and self-administered forms. There is a combination of standardised and non-standardised outcome measures that will be used as part of the registry. Data for both parts of the AMC registry are collected on the child, the biological mother and the biological father.

For the child, information regarding complications during the first month of life, documentation of medical procedures and comorbidities,[14] type and severity of contractures, other birth defects and phenotypic presentation will be collected. Risk factors, including consanguinity, pregnancy complications, biological parents' lifestyle and family history will also be collected. Data sources include case report forms completed via a telephone interview with the primary caregiver, a medical chart review, a review infant and current photographs and a pedigree chart when available. Estimated time from the previous pilot study[14] to collect the data is between 1 and 3 hours depending on the age-specific outcome measures to be completed.

Outcome measures

The CRC at each site will coordinate the completion of the following measures and questionnaires during the clinic visit, via telephone, videoconferencing or electronically through Qualtrics XM, a secure online survey platform that can be distributed to families who prefer to complete the questionnaires independently at their own time. For a complete list of outcomes collected for Part 1, refer to table 1.

Mobility will be assessed using the Functional Mobility Scale (FMS) and the Gillette Functional Assessment Questionnaire (FAQ). The FMS is a free, standardised outcome measure developed to classify functional mobility validated for children with cerebral palsy. It considers the assistive devices a child may use to mobilise in the home, at school and in the community settings. It is a performance measure done by the clinician interviewing the child/parent.[18] While it was designed for children with

Table 1 List of all the outcomes collected for Part 1

Standardised outcome measures*	Patient-reported outcomes ▶ Ages & Stages Questionnaire ▶ Functional Mobility Scale ▶ Adolescent and Pediatric Pain Tool ▶ Gillette Functional Walking Subscale ▶ EuroQOL-5D-Youth ▶ Patient-Reported Outcomes Measurement Information System
	Clinician-administered outcomes ▶ The Functional Independence Measure for Children ▶ Passive range of motion (as per standard of care)
AMC Registry Specific Questionnaires	Demographic form ▶ Pregnancy and Newborn Questionnaire ▶ History of interventions ▶ Medical records extraction form (pregnancy, delivery, newborn, genetics) ▶ Photograph Checklist ▶ Description of contractures

*Administration of outcome measures is based on participants' age.
AMC, arthrogryposis multiplex congenita.

cerebral palsy, considering children with AMC often rely on assistive devices to walk and have limited ambulation potential and has been used in previous research in children with AMC,[19] it was selected to provide a standardised description of functional mobility for the registry. The FMS will be completed on participants between 4 and 21 years of age and is scored for each distance of 5, 50 and 500 m. The FAQ is a 10-level parent-report scale describing ambulation level (from independent community ambulation to nonambulatory) for children with walking disabilities.[20] As such, it will be completed on participants between 2 and 21 years of age, providing one score ranging from 1 to 10.

The Functional Independence Measure for Children (*WeeFIM*) instrument examines basic daily living and functional skills in children from birth to 7 years of age, and includes 18 items in the following subscales: self-care, sphincter control, transfers, locomotion, communication and social cognition. The WeeFIM was designed as either an observational or interview instrument. Some items are easily observed (eg, walking up stairs); others are more difficult to observe (eg, sphincter control).[21] Self-care, mobility, cognition and total scores will be computed. For the purposes of this study, the interview will be conducted with the parent or other caregiver who is familiar with the child, and the child between 3 and 21 years of age by certified personnel. A CRC and/or rehabilitation specialist at each participating site will complete the training and credentialing to administer and score the WeeFIM. An inter-rater reliability exercise will be completed by viewing two recordings depicting the administration of the WeeFIM with two children, and scoring the individual items. Subscales, domains and total scores will be calculated and interrater reliability will be computed using the Kappa statistic for individual items and the intraclass correlation (ICC) for subscales, domains and total scores.[22] If raters achieve ICC values below 0.80, a training session to go over scoring will be provided to promote greater agreement.

Ages & Stages Questionnaire is a developmental screening to be completed with parents of children 0–66 months of age and is available in English, French and Spanish. It is a parent-completed developmental screening tool that covers the domains of communication, gross motor, fine motor, problem solving and personal-social.[23]

Adolescent and Pediatric Pain Tool is a self-report assessment to be completed by youth between 8 and 21 years to describe number of pain sites, pain intensity and pain descriptors.[24]

EuroQOL-5D-Youth to be completed by youth between 8 and 21 years and parents of children 4–18 years of age to describe the child's quality of life. In the case that a youth 18–21 years of age is unable to complete the questionnaire (eg, cognitive impairment), the parent would complete the parent-proxy questionnaire.[25]

Patient-Reported Outcomes Measurement Information System subscales for pain interference, mobility, upper extremity and peer relationship short form to be completed by the primary caregiver of children 5–17 years (Parent Proxy Item Bank V.2.0) and by capable youth 8–17 years (Pediatric Item Bank V.2.0). When possible, young adults 18–21 years will be asked to complete the short forms for Pain Interference V.1.0 8a, Physical Function V.2.0 8b, Upper Extremity V.2.0 7a, Satisfaction with Social Roles and Activities V.2.0 8a.[26]

Clinical genetics

The following criteria are used to determine eligibility for WGS: family history of isolated or multiple contractures, consanguinity, atypical clinical presentation (asymmetrical contractures for example), multisystem involvement, intellectual disability/developmental delays, negative finding on prior genetic testing or absence of prior genetic testing. In the case of prior genetic testing, parents are asked to complete an authorisation to release medical records to receive the genetic testing results. As part of data collection, the CRC staff at each site will also construct the child's pedigree up to two generations for

Table 2 Age of consent at participating Shriners Hospitals for Children

Site	Age of informed consent (years)	Age of assent (years)
Canada	14 and older	7–13
California	18 and older	7–17
Chicago	18 and older	7–17
Greenville	15 and older	7–14
Honolulu	18 and older	7–17
Portland	15 and older	7–14
Philadelphia	18 and older	7–17

the purposes determining if other family members are similarly affected. Patient photographs obtained by participating centres including facial features, spine and joint contractures will also be obtained. A registry-specific data sheet to record specific dysmorphic features observed on these photographs is completed by the consulting geneticist. These criteria will be reviewed with the team at each site and the consulting geneticist using a remote teleconferencing platform. Participants eligible for WGS testing will be invited by the CRC at each site to provide a saliva sample as well as from the biological parents to obtain a trio analysis. Additional family members may be invited to provide a saliva sample should they present with congenital contractures to assist with determination of Mendelian segregation of observed DNA sequence variants. On obtaining signed informed consent for the participant and family members, the CRC will provide a saliva sampling kit to participants enrolled. If the biological family members and/or child is/are not available in person at the hospital, a saliva kit will be provided by mail or in person. In this case, the consent discussion will be held over the telephone. A signed version of the consent form will be mailed or emailed back to the CRC prior to the analysis of the sample. DNA or saliva kits collected will be sent to the Shriners Hospitals Genomics Institute in Tampa, Florida, USA for sequencing. Shriners Hospitals has an Illumina Enterprise cloud-based space where the data will become available to the bioinformatician for analysis using the TruSight platform on Illumina. The analysis will target the identification of known genes[27] as well as de novo mutations by excluding those present in the genomes of the parents. Potential variants outside the exonic and splice consensus regions will be excluded if they are present in small-repeat regions (for single-nucleotide variants and insertions and deletions (indels)), or in Alu regions (for indels). To assess whether candidate de novo mutations are pathogenic, we will use a statistical framework that determines the rate of de novo variants per gene per class of variant in order to determine whether there is gene enrichment for a particular variant class in the studied cohort and thus provide evidence that the observed mutations are most likely implicated in AMC. Copy Number Variations (CNVs) will be identified,[28 29] with CNVs falling in regions of segmental duplications being excluded. To identify de novo CNVs in-patient DNA, we will exclude those CNVs that are present in any of the parents' samples. De novo CNVs will be prioritised for validation only if they affect exonic regions and if they cannot be ruled out as inherited or false positives on visual inspection by integrative genomic viewer (IGV) of the reads near breakpoints. CNVs will be validated in the trio by other sequencing technologies, such as TaqMan assay Sanger sequencing of breakpoints, or array comparative genomic hybridization (CGH). Variant identification will be done by first looking at known AMC genes as published by Kiefer and Hall[27] and updated by an international gene panel curation international consortium.[30] In cases where no known gene is identified, variants will be grouped to identify common variants in unrelated families. In the latter case, variant prioritisation will be done using typical parameters, such as frequency in gnomAD, prediction of damage to protein function as per prediction algorithms. Matchmaker Exchange will be used to discover novel disease–gene relationships.

Data management

The data collected in case report forms will be entered in a secure electronic database called Advarra EDC. This common method of data entry facilitates easy access to the comprehensive inventory of information and enables sharing between facilities on secured servers. A data monitoring committee is not assigned to this registry as no adverse events are expected since no interventions will be administered to participants as part of this registry. Data will be secured and password protected and only accessed by registry personnel. Essential to standardised data collection will be a manual of operations for each part of the registry (Part 1: epidemiology, etiology and interventions; Part 2: genomics), which includes detailed data collection procedures, a data dictionary, documentation requirements, validation rules and enhanced International Classification of Diseases (ICD)-10 codes to ensure straightforward data retrieval. Since this registry is not publicly funded, data are currently available only to participating investigators. An international collaboration is underway to identify common data elements for AMC to guide a uniform data collection towards an international registry. In order to share data with the participants, their families and approved healthcare professionals and researchers, a data access procedure is required so that data may be shared while personal, identifying information will be kept private in adherence with local regulations (ie, Health Insurance Portability and Accountability Act, General Data Protection Regulation). Such efforts also warrant devising legal and ethical frameworks along with intellectual property attribution, as well as addressing potential issues related to processing of data, data extraction and conducting analyses using registry data.

Data analysis plan

Descriptive statistics will be used to summarise relevant data regarding frequency, risk factors, interventions and functional status of children with AMC. These will be reported as means, medians and proportions with corresponding measures of error as deemed appropriate. Qualitative analysis will also be used to describe the various phenotypes of AMC conditions. Descriptive analysis will be used to describe type and frequency of treatments, as well as outcomes (self-care, mobility, pain). The AMC registry will assist in generating and conducting hypothesis-driven research led by clinicians and researchers. Appropriate statistical analyses will be conducted depending on the research design selected. For instance, to evaluate the association between type of intervention and outcome, logistic regression models will be calculated for each outcome measure and adjusted for surgical treatment (yes/no), non-surgical treatment (yes/no), baseline function, age and joint involvement (minimal, moderate, severe). Finally, a descriptive analysis of the genotypes identified and a correlation with the phenotypic expression of the various genes will be conducted.

Ethics and dissemination

Administrative site approval was obtained for the registry from the Department of Medical Research at Shriners Hospitals for Children Sponsor (CAN79150). As well, research ethics and administrative site approvals have been received at both SHC-Canada (McGill University Faculty of Medicine Institutional Review Board A08-M30-19B) and all participating US sites through WCG (WIRB and Copernicus Group IRB #20191755). Ethical approval was sought prior to the commencement of any data collection. Since the registry is not a clinical trial, this protocol has not been registered. As Part 1 of the registry is considered minimal risk, the local ethics boards granted a waiver of written consent. As such, only verbal consent is required prior to participation and can be obtained by the CRC assigned to the study either face-to-face or remotely (ie, over the telephone). As Part 2 of this study involves sharing and analysis of genetic information, informed written consent is required. Both consent processes are documented on a specific form to log the procedure followed and date consent was received. See table 2 for list of ages of consent and assent according to various participating sites. This consent will be obtained while the patients are present for AMC clinic by the CRC assigned to the study. Either or both parents/guardians will sign the consent form as they will be the ones to complete the questionnaire over the telephone. For the Canadian site, assent will be obtained for children between the ages of 7 and 14. For patients older than 14 years of age, consent will be obtained from both the parent and the child to ensure participation. In the US sites, children between the ages of 7 and 17 provide assent while those over 18 years of age provide consent. These procedures are state and province specific and are approved by the local research ethics boards. Should a patient become 14 (Canadian site) or 18 (American sites) during the course of the study, the CRC will contact the patient to obtain consent.

Closure of registry and sustainability

The funding obtained by the Shriners Hospitals for Children for the implementation of the registry at the seven hospital sites extends to December 2022. Additional funding was secured (2021–2023) through the American Society for Bone and Mineral Research to expand the registry at the international level. In 2022, the research team will develop a plan for sustainability of the registry, including funding from other sources, further refinement to procedures to minimise burden while maximising data quality. As resources and costs of maintaining such a registry include submitting, obtaining and maintaining ethical approvals at participating sites, recruitment, data collection and entry, as well as technological supports to house the data, a sustainability plan requires consideration to all these elements. In addition, findings from the registry will inform hypothesis-driven research which will be used to leverage funding for research advancement.

DISCUSSION

The AMC registry is designed to provide the platform for multicentre research studies on the epidemiology, aetiology, interventions and genomics in AMC. It is the first cross-sectional study done in paediatric AMC on large sample that can provide important information on aetiology and natural history. To date, most research conducted in AMC has been retrospective chart reviews and thus, the registry provides the first prospective design for this population. Evidence and effectiveness of various therapies (genetic, surgical and rehabilitative) is lacking. Considering the rarity of AMC and the heterogeneity of the population, large sample sizes to conduct research with generalisable outcomes are nearly impossible to gleam from single-site studies. Multisite collaborations not only increase sample sizes but can also generate hypothesis-driven research questions that can benefit the entire paediatric AMC population.

The AMC registry also provides the opportunity to identify genes that may be responsible for AMC through the use of WGS. While the results need to be validated clinically, this would be the first large scale attempt to associate genotype with phenotype and create subgroups within this population. Future international collaborations will be useful in further increasing sample size as well as other medical professionals who work with this population (eg, neurology, developmental paediatrics, neonatology and so on). We anticipate that the lessons learnt from this registry lead to international collaborations and funding opportunities to execute hypothesis-driven research for AMC.

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Contributors ND-O, RCH, TB, JH and HvB initiated and planned this study as well as developed all associated materials. ND-O, TB, VBD, RCH, HvB, FR, PG wrote the protocol and the paper. ND-O, RCH, TB, HvB, MJ, ER, KF, HA, JP, LH, PG and JH obtained funding. All authors read and approved the final version of this paper. FR, GB and PG will conduct genetic analyses. ND-O, RCH, HvB, MJ, KF, HA, JP, LH, ER will conduct the registry.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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REFERENCES

1 Dahan-Oliel N, Cachecho S, Barnes D, *et al*. International multidisciplinary collaboration toward an annotated definition of arthrogryposis multiplex congenita. *Am J Med Genet C Semin Med Genet* 2019;181:288–99.
2 Skaria P, Dahl A, Ahmed A. Arthrogryposis multiplex congenita *in utero*: radiologic and pathologic findings. *J Matern Fetal Neonatal Med* 2019;32:502–11.
3 Kimber E. AMC: amyoplasia and distal arthrogryposis. *J Child Orthop* 2015;9:427–32.
4 Binkiewicz-Glinska A, Sobierajska-Rek A, Bakula S, *et al*. Arthrogryposis in infancy, multidisciplinary approach: case report. *BMC Pediatr* 2013;13:184.
5 Hansen-Jaumard D, Elfassy C, Montpetit K, *et al*. A review of the orthopedic interventions and functional outcomes among a cohort of 114 children with arthrogryposis multiplex congenita. *J Pediatr Rehabil Med* 2020;13:263–71.
6 van Bosse HJP, Feldman DS, Anavian J, *et al*. Treatment of knee flexion contractures in patients with arthrogryposis. *J Pediatr Orthop* 2007;27:930–7.
7 van Bosse HJP, Marangoz S, Lehman WB, *et al*. Correction of arthrogrypotic clubfoot with a modified Ponseti technique. *Clin Orthop Relat Res* 2009;467:1283–93.
8 Yang SS, Dahan-Oliel N, Montpetit K, *et al*. Ambulation gains after knee surgery in children with arthrogryposis. *J Pediatr Orthop* 2010;30:863–9.
9 Augustine EF, Adams HR, Mink JW. Clinical trials in rare disease: challenges and opportunities. *J Child Neurol* 2013;28:1142–50.
10 Todd EJ, Yau KS, Ong R, *et al*. Next generation sequencing in a large cohort of patients presenting with neuromuscular disease before or at birth. *Orphanet J Rare Dis* 2015;10:148.
11 Dieterich K, Kimber E, Hall JG. Central nervous system involvement in arthrogryposis multiplex congenita: overview of causes, diagnosis, and care. *Am J Med Genet C Semin Med Genet* 2019;181:345–53.
12 Bamshad M, Jorde LB, Carey JC. A revised and extended classification of the distal arthrogryposes. *Am J Med Genet* 1996;65:277–81.
13 Bedard T, Lowry RB. Disease coding systems for arthrogryposis multiplex congenita. *Am J Med Genet C Semin Med Genet* 2019;181:304–9.
14 Dahan-Oliel N, Bedard T, Darsaklis VB, *et al*. Development of a research platform for children with arthrogryposis multiplex congenita: study protocol for a pilot registry. *BMJ Open* 2018;8:e021377.
15 Dahan-Oliel N, van Bosse HJP, Bedard T, *et al*. Research platform for children with arthrogryposis multiplex congenita: findings from the pilot registry. *Am J Med Genet C Semin Med Genet* 2019;181:427–35.
16 Ravenscroft G, Clayton JS, Faiz F, *et al*. Neurogenetic fetal akinesia and arthrogryposis: genetics, expanding genotype-phenotypes and functional genomics. *J Med Genet* 2021;58:609–18.
17 Laquerriere A, Jaber D, Abiusi E, *et al*. Phenotypic spectrum and genomics of undiagnosed arthrogryposis multiplex congenita. *J Med Genet* 2022;59:559–67.
18 Graham HK, Harvey A, Rodda J, *et al*. The functional mobility scale (FMS). *J Pediatr Orthop* 2004;24:514–20.
19 Altiok H, Flanagan A, Krzak JJ, *et al*. Quality of life, satisfaction with life, and functional mobility of young adults with arthrogryposis after leaving pediatric care. *Am J Med Genet C Semin Med Genet* 2019;181:461–8.
20 Novacheck TF, Stout JL, Tervo R. Reliability and validity of the Gillette functional assessment questionnaire as an outcome measure in children with walking disabilities. *J Pediatr Orthop* 2000;20:75–81.
21 Ottenbacher KJ, Msall ME, Lyon NR, *et al*. Interrater agreement and stability of the functional independence measure for children (WeeFIM): use in children with developmental disabilities. *Arch Phys Med Rehabil* 1997;78:1309–15.
22 Cronbach LJ, Gleser GC, Nanda H. *The dependability of behavioral measurements: theory of generalizability for scores and profiles*. New York: Wiley, 1972.
23 Squires J, Bricker D. (ASQ®-3): A Parent-Completed Child Monitoring System. In: *Ages & Stages Questionnaires®*. Third Edition. Baltimore: Paul H. Brookes Publishing Co., Inc, 2009.
24 Savedra MC, Tesler MD, Holzemer WL. *Adolescent Pediatric Pain Tool (APPT): User's manual*. San Francisco, CA: University of California, School of Nursing, 1995.
25 Wille N, Badia X, Bonsel G, *et al*. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Qual Life Res* 2010;19:875–86.
26 Cella D, Yount S, Rothrock N, *et al*. The patient-reported outcomes measurement information system (PROMIS): progress of an NIH

roadmap cooperative group during its first two years. *Med Care* 2007;45:S3–11.
27 Kiefer J, Hall JG. Gene ontology analysis of arthrogryposis (multiple congenital contractures). *Am J Med Genet C Semin Med Genet* 2019;181:310–26.
28 Layer RM, Chiang C, Quinlan AR, *et al*. LUMPY: a probabilistic framework for structural variant discovery. *Genome Biol* 2014;15:R84.
29 Hamdan FF, Myers CT, Cossette P, *et al*. High rate of recurrent de novo mutations in developmental and epileptic encephalopathies. *Am J Hum Genet* 2017;101:664–85.
30 Stark Z, Foulger RE, Williams E, *et al*. Scaling national and international improvement in virtual gene panel curation via a collaborative approach to discordance resolution. *Am J Hum Genet* 2021;108:1551–7.