BMJ Open

Development of a research platform for children with arthrogryposis multiplex congenita: Study protocol for a pilot registry.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-021377
Article Type:	Protocol
Date Submitted by the Author:	11-Jan-2018
Complete List of Authors:	Dahan-Oliel, Noémi; Shriners Hospitals for Children Canada, Clinical research; McGill University, School of Physical and Occupational Therapy Bedard, Tanya; University of Calgary and Alberta Health Services Department of Paediatrics Darsaklis, Vasiliki Betty; Shriners Hospitals for Children Canada, Rehabilitation Hall, Judith; BC's Children's Hospital, Medical Genetics van Bosse, Harold; Shriners Hospitals for Children Philadelphia Hamdy, Reggie; Shriners Hospitals for Children Canada, Clinical research; McGill University, Faculty of Medicine, Department of Orthopedics
Keywords:	Paediatric orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, STATISTICS & RESEARCH METHODS, Paediatric clinical genetics & dysmorphology < GENETICS, EPIDEMIOLOGY

Title page

Manuscript title:

Development of a research platform for children with arthrogryposis multiplex congenita: Study protocol for a pilot registry

Corresponding author:

Noémi Dahan-Oliel, PhD, OT

Clinical Research Department, Shriners Hospital for Children-Canada

1003 Decarie Boulevard

Montreal, Quebec H4A 0A9, Canada

Telephone: 514-842-4464 extension 2278

Fax: 514-842-7553

Email: ndahan@shrinenet.org

Authors' names and addresses:

Noémi Dahan-Oliel[1,2], Tanya Bedard[3], Vasiliki Betty Darsaklis[1], Judith Goslin Hall[4], Harold J.P. van Bosse[5], Reggie Charles Hamdy[1,6]

1. Shriners Hospital for Children, Montreal, Canada
   1003 Decarie Boulevard
   Montreal, Quebec H4A 0A9, Canada
2. School of Physical and Occupational Therapy, McGill University, Montreal, Canada
   3654 Promenade Sir-William-Osler
   Montreal, Quebec H3G 1Y5, Canada
3. Alberta Congenital Anomalies Surveillance System
   Alberta Health, Alberta Children's Hospital
   288 Shaganappi Trail NW
   Calgary, AB T3B 6A8, Canada
4. Department of Medical Genetics and Department of Pediatrics,
   University of British Columbia and BC Children's Hospital,

Room C234
4500 Oak Street
Vancouver, BC V6H 3N1, Canada

5. Shriners Hospital for Children, Philadelphia, USA
3551 North Broad Street
Philadelphia, PA 19140, USA

6. Department of Pediatric Surgery
McGill University Health Centre
The Montreal Children's Hospital
1003, boulevard Décarie, Suite 6.59A
Montréal, Québec H4A 0A9, Canada

Word count: 2093

Development of a research platform for children with arthrogryposis multiplex congenita: Study protocol for a pilot registry

ABSTRACT

Introduction. Arthrogryposis multiplex congenita (AMC) describes a heterogeneous group of conditions with multiple congenital contractures. AMC may be attributed to genetic or other factors inducing decreased fetal movements, including maternal factors and paternal influences. Discovering the genetic pathways responsible for AMC has important repercussions for prevention, gene therapy and genetic counseling. The current literature mainly consists of small-scale, single-site studies, limiting comparability and pooling of findings across individual studies. To provide the framework for the international AMC registry needed to support high quality studies to drive this field forward at both the epidemiologic and clinical levels, a multicenter pilot registry for children with AMC will be developed. **Methods and analysis.** Forty families of children from birth to 21 years of age with AMC will be invited to join the registry for the pilot phase. Data will be collected on the child (demographic and newborn variables), mother and father (demographic, lifestyle habits and medical history). To promote standardized data collection, an operations manual will be developed. Descriptive statistics will be used to summarize relevant data, regression analyses will be used to determine associations to generate hypotheses regarding factors contributing to AMC. Qualitative analysis will also be used to better describe phenotypical presentation of AMC. **Ethics and dissemination.** Ethics approval was obtained at the participating sites. The pilot registry for children with AMC will provide the platform for a comprehensive

international AMC registry that will generate multiple research avenues to enhance current care and establish new therapies. Following this pilot study, the participant selection criteria will be refined, data sets will be expanded to include rehabilitation, surgical management and long-term outcomes, and the best timing for the questionnaire administration and frequency of follow-up prior to fully implementing the international AMC registry will be determined.

Strengths & Limitations

- An international multidisciplinary team of experts contributed to the development of this registry.
- This is the first registry of its kind for AMC.
- Sustainability of any registry is dependent on funding.
- This registry is initially an observational study and will not be comparing various treatment options.

INTRODUCTION

Arthrogryposis and arthrogryposis multiplex congenita (AMC) are descriptive terms, rather than specific diagnoses, used for a heterogeneous group of conditions with multiple congenital contractures and are often used interchangeably. This group of conditions affect 1 in 3000 live births[1,2] and result from a lack of fetal movement[3] Individuals born with AMC exhibit multiple joint contractures in at least two different body areas, including the upper and lower limbs, spine and jaw.[1] They represent complex cases as impairments in other systems including gastro-intestinal, genito-urinary and central nervous systems are common.[4]

Hall,[5] recommended classifying cases using the following categories to aid in a specific diagnosis in AMC: i) limb involvement only, ii) limb with other system involvement, and iii) neuromuscular involvement with central nervous system dysfunction or intellectual disability. A specific diagnosis is based on the evaluation of pregnancy and delivery history, a detailed physical examination with documentation as to which joints are affected and the degree of extension and/or flexion, the examination of radiographs and photographs, and the natural history of complications in response to different interventions.[5] Laboratory tests, such as muscle biopsies, blood tests, and genetic analysis, also contribute to a specific diagnosis.

AMC may occur as part of inherited single-gene disorders or may occur sporadically. Currently, over 300 genes have been associated with AMC;[6,7] however, it is unclear how these mutations lead to the clinical presentation of AMC as less than half of patients have a mutation in one of the known AMC-related genes.[8] Discovering the genetic pathways responsible for this condition has important repercussions for

prevention, gene therapy and genetic counseling. AMC may also be attributed to other factors inducing decreased fetal movements. These include maternal factors such as structural uterine anomalies that result in fetal crowding, exposure to teratogens, maternal conditions (such as myasthenia gravis and multiple sclerosis) and physical health status at time of conception and during gestation. Paternal influences may also play a key role and need to be studied further.[9,10]

Factors integral to understanding the long-term needs of individuals with rare conditions, such as individuals with AMC, relate to the epidemiology and natural history and are lacking in the literature. The terminology and definitions used by various disciplines to classify and describe this group of conditions and applied outcome measures are often inconsistent. The International Classification of Diseases (ICD), a standard diagnostic tool used in epidemiology, and health management does not provide the necessary details to easily retrieve cases with a specific AMC condition for research and clinical purposes, nor does it indicate severity or etiological information.

Research studies in AMC are often fragmented, isolated, and are small-scale. Conducting research in rare diseases poses several challenges. Investigator-initiated research often results in small sample sizes,[11] precluding the use of robust statistical methods and limiting the findings' external validity. Comparability and pooling of findings across individual studies in rare diseases often lack standardization in methodology and will vary in data collection, selection criteria, classification and outcome measures used.[12]

Currently there is no comprehensive registry or classification system to support the high quality studies needed to forward this field at both the epidemiologic and clinical

levels. Collaborations at the international level across a breadth of disciplines offer enormous scientific leveraging opportunities. The creation and implementation of an international multi-site AMC registry will provide the opportunity to collaborate and develop standardized methodologies to contribute to rigorous research and enhance current care and establish new therapies. Prior to the full implementation of the international AMC registry, a pilot registry will be developed.

The aims of the pilot registry for AMC are to:

- Provide the framework to fully implement the international AMC registry
- Provide opportunities to refine participant selection criteria, and expand data sets to include rehabilitation, surgical management and long term outcomes
- Determine the best timing of questionnaire administration and frequency of follow-up
- Resolve potential challenges before the full implementation of the international AMC registry

METHODS AND ANALYSIS

Study design

The pilot registry is a retrospective (cross-sectional) multicenter registry. This registry was initiated by a consortium of experts which identified the gaps in research and clinical therapies for children with AMC. The consortium included six members from a variety of disciplines: rehabilitation, genetics, orthopedics, clinical research and registry management. Additionally, patient representativeness was ensured through the inclusion

of a patient advocate. Prior to full registry implementation, the registry will be pilot tested. Pilot testing is crucial in determining the feasibility of a study prior to launching a large-scale multi-site, international project. It allows the investigators to solve potential issues prior to full expansion. Figure 1 represents the timeline for the pilot registry and its projection.

Study Setting and participant eligibility

The pediatric AMC registry will be pilot tested at two Shriners Hospital for Children (SHC) sites: the SHC-Canada in Montreal, Quebec and SHC-Philadelphia. These two sites were purposefully selected as they have a large population of patients with AMC thus facilitating recruitment. Additionally, their geographic and multicultural diversity will provide the unique opportunity to explore genetic and environmental influences on the frequency of AMC for the pilot phase. Prior to piloting, a standardized training module will be used to ensure that recruitment, data collection and interpretation are performed in a consistent manner across both recruiting sites. Once training is complete, pilot testing will commence by recruiting 20 families from each site. Families will be recruited based on having a child (0-21 years old) with AMC.

Informed consent and research ethics

Patient participation is completely voluntary, and informed written consent will be obtained prior to participation. Research ethics and administrative site approvals have been received at both the SHC-Canada and SHC-Philadelphia sites.

Data Collection

Data collection will be performed locally and anonymized for name in the online OnCore Enterprise Research software. OnCore is used in all SHC studies. This is a secure

database and is backed up regularly. Specific individual information in the registry will not be shared with other persons, entities or companies unless obligated by legal authorities.

For the pilot phase, data will be collected from both the medical chart and from an interview with the study research assistant and the primary caregiver. The information collected from the two sources will be compared statistically (using Cronbach's alpha) so that the agreement between the two sources can be established. If the agreement is high (over 70 percent), only the interview with the primary caregiver will be retained. If larger discrepancies exist for certain data sets, the medical charts for those specific data points will be requested. The source document (either chart review or interview with caregiver) will therefore be determined a priori based on this comparison. By minimizing medical chart requisitions, data collection will be facilitated in the larger scale implementation. The data collected will be entered by the research assistant in the Case Report Form (CRF) which in turn will be used to populate OnCore. This common method of data entry facilitates easy access to the comprehensive inventory of information and enables sharing between facilities on secured servers.[13]

Essential to standardized data collection will be the operations manual which will include detailed data collection procedures, a data dictionary, documentation requirements, validation rules, and enhanced ICD-10 codes to ensure straightforward data retrieval.

Case definition

A clear and standardized case definition is necessary to ensure that all potential participants of the registry can be systematically and correctly identified and approached

for recruitment. Considering the heterogeneity of the AMC population, as well as the lack of proper coding systems within healthcare institutions to properly denote individuals with AMC,[2] a specific case definition was developed through consultation with a panel of experts on AMC and registry development. This definition includes a description of AMC, onset, factors associated with AMC, clinical presentation, as well as functional and long-term implications.

Data elements

The final data set for the pilot registry was validated through the method proposed by Lawshe.[14,15] Content validation of any instrument is crucial prior to piloting its use to ensure that an instrument covers the universe of the content but is free of unwanted or irrelevant details for the overall purpose.[16] Validation of the data set is essential to ensure that the information collected will be pertinent to ultimate end users of the knowledge (clinicians, families, patients). The final data set only includes items with high content validity ratios, thereby increasing the efficiency and significance of the data elements for the pediatric AMC registry. The specifics of this method as well as the results of the exercise will be shared through another publication.

For the pilot phase of this study, data will be collected on the child (date of birth, place of birth, newborn variables including but not limited to birthweight and gestation, race and ethnicity, diagnoses), maternal and paternal demographics (date of birth, residence, ethnicity, lifestyle habits) and on the medical history (preexisting conditions, prescription use), pregnancy (antenatal conditions), birth (delivery information). See figure 2 for a complete list of the data sets. Initial data sets were developed through

consultation with the consortium of experts. The pilot registry for AMC in pediatrics was modelled after the established Canadian Cerebral Palsy registry and tailored for the AMC population using the most updated, comprehensive reference manual "Arthrogryposis: A Text Atlas".[17] This resulted in a comprehensive, AMC-specific CRF.

Statistical Analysis

Descriptive statistics will be used to summarize relevant data. These will be reported as means, medians, numbers, or proportions with corresponding measures of error as deemed appropriate. Regression analyses will be used to determine associations to generate hypotheses regarding factors contributing to AMC which will be tested in the international AMC registry. Qualitative analysis will also be used to better describe phenotypical presentation of AMC.

Closure of Registry

The pilot phase of the pediatric AMC registry will end once 40 families have been recruited amongst the two participating sites. Recruitment procedures will be evaluated and preliminary data analysis will be completed. Expansions to the registry content as well as to participating sites will be reviewed with the consortium.

DISCUSSION

The pilot AMC registry is designed to provide the platform for multi-center, standardized and longitudinal research studies in AMC. To date, little is known about AMC with respect to etiology and natural history. 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

generalizable outcomes is nearly impossible to gleam from single-site studies. International, multi-site collaboration is warranted and can be achieved through an international registry. A standard case definition is essential in ensuring that all potential participants are consistently targeted across sites so that sample size can be as large as possible. A rich CRF is crucial in gathering all salient information required for future research avenues with AMC. The creation of an operational manual will facilitate the implementation of an AMC registry by providing standardization regarding data collection procedures as well as definitions and enhanced ICD-10 codes to be used for cases with different types of AMC. The generation of an online database that can be shared between sites will facilitate data collection, analysis and interpretation.

Considering the novelty of this approach with this population, a pilot phase of the initial registry for AMC is necessary to test feasibility (including need for personnel training) and impact on families. Piloting the registry for AMC on 40 participants across 2 SHC sites will provide important information with respect to ease of recruitment, length of administration, and ease of execution. Random audits on 20% of the data registry (4 at each site) will contribute to data quality assurance. These are the final steps required prior to implementing a large-scale, multi-site international AMC registry, which will provide the foundation for pursuing evidence-based interventions.

SUMMARY

Establishing a pilot AMC registry will provide the platform for a full expansion of the AMC registry to generate multiple research avenues to enhance current care and establish new therapies. Following this pilot study, we will refine the participant selection

criteria and determine the best timing for the questionnaire administration and frequency of follow-up. As AMC includes a group of rare conditions, this protocol will also serve to guide the establishment of future rare disease registries.

Figure Legends

Figure 1. Timeline for the pilot registry and projection.

Figure 2. List of data sets for the pilot registry

Author's contributions

NDO, RH, TB, HvB, and JH initiated and planned this study as well as developed all associated materials. **NDO, TB, VD** wrote the protocol and the paper**. NDO, RH, TB, HvB, JH** obtained funding. All authors read and approved the final version of this paper. **NDO, RH and HVB** will conduct the pilot phase of the registry.

Funding

The development of the data sets, content validity and pilot phases are funded by a Developmental Clinical Grant from the Shriners Hospitals for Children grant number 79150. The planning activities and face-to-face meeting for the consortium of experts were funded by a planning and dissemination grant from the Canadian Institutes of Health Research – Institute of Musculoskeletal Health and Arthritis grant number 144020.

Competing interests

The authors report no competing interests.

Acknowledgments

The authors acknowledge the administrative support of Carla Evangeliste and Nicole Young, graphic and medical illustrations by Guylaine Bédard and Denis Alves, and the scientific contribution of Dr. Bonita Sawatzky, Kathleen Montpetit, Caroline Elfassy, Rita Yap, Emily Lecker, Dr. Maryam Oskoui, Dr. Amy Metcalfe, Dr. Eva Ponten, Dr.

Douglas Barnes, Dr. Patricia Mills, Dr. Brian Lowry, Dr. Reid Nichols and Hirmand Nouraei.

References

1. Hall JG. Arthrogryposis multiplex congenita: etiology, genetics, classification, diagnostic approach, and general aspects. *J Pediatr Orthop B* 1997 Jul;6(3):159-66.
2. Lowry RB, Sibbald B, Bedard T, et al. Prevalence of multiple congenital contractures including arthrogryposis multiplex congenita in Alberta, Canada, and a strategy for classification and coding. *Birth Defects Res A Clin Mol Teratol* 2010 Dec;88(12):1057-61. doi: 10.1002/bdra.20738. [Published online First: 15 November 2010].
3. Bevan WP, Hall JG, Bamshad M, et al. Arthrogryposis multiplex congenita (amyoplasia): an orthopaedic perspective. *J Pediatr Orthop* 2007 Jul-Aug;27(5):594-600.
4. Bernstein RM. Arthrogryposis and Amyoplasia . *J Am Acad Orthop Surg* 2002 Nov-Dec;10(6):417-24
5. Hall JG. Arthrogryposis (multiple congenital contractures): Diagnostic approach to etiology, classification, genetics, and general principles. *Eur J Med Genet* 2014 Aug;57(8):464-72 doi: 10.1016/j.ejmg.2014.03.008 [Published online First: 3 Apr 2014].
6. Hall JG. Genetic aspects of arthrogryposis. *Clin Orthop Relat Res* 1985 Apr;(194):44-53.
7. Hunter JM, Kiefer J, Balak CD, et al. Review of X-linked syndromes with arthrogryposis or early contractures-aid to diagnosis and pathway identification.

Am J Med Genet A 2015 May;167A(5):931-73 doi: 10.1002/ajmg.a.36934 [Published online First: 19 March 2015].

8. Bamshad M, Van Heest AE, Pleasure D. Arthrogryposis: a review and update. *J Bone Joint Surg Am* 2009 Jul;91(Suppl 4):40-6 doi: 10.2106/JBJS.I.00281
9. Reddihough DS, Collins KJ. The epidemiology and causes of cerebral palsy. *Aust J Physiother* 2003;49(1):7-12.
10. Feinberg JI, Bakulski KM, Jaffe AE, et al. Paternal sperm DNA methylation associated with early signs of autism risk in an autism-enriched cohort. *International Journal of Epidemiology* 2015 44(4)1199–1210 https://doi.org/10.1093/ije/dyv028 [Published online First: 1 August 2015]
11. Augustine EF, Adams HR, Mink JW. Clinical trials in rare disease: challenges and opportunities. *J Child Neurol* 2013 Sep;28(9):1142-50 doi: 10.1177/0883073813495959
12. Griggs RC, Batshaw M, Dunkle M, et al. Clinical research for rare disease: Opportunities, challenges, and solutions. *Mol Genet Metab* 2009 Jan;96(1):20-6 doi: 10.1016/j.ymgme.2008.10.003. [Published online First: 13 November 2008]
13. Gliklich R, Dreyer N, Leavy M, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. Two volumes. (Prepared by the Outcome DEcIDE Center [Outcome Sciences, Inc., a Quintiles company] under Contract No. 290 2005 00351 TO7.) AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April

2014. http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm. (accessed 15 December 2017)

14. Lawshe CH. A Quantitative Approach to Content Validity. *Personnel Psychol* 1975;28(4):563–75 doi: 10.1111/j.1744-6570.1975.tb01393 [Published online: 7 December 2006]
15. Wilson FR, Pan W, Schumsky DA. Recalculation of the critical values for Lawshe's content validity ratio. *Measurement and Evaluation in Counseling and Development* 2012 45(3), 197-210 doi:10.1177/0748175612440286. [Published online: 10 Mar 2017]
16. Portney LG, Watkins MP. Foundations of clinical research: Applications to practice (3rd ed.). Upper Saddle River, NJ: Pearson & Prentice Hall 2009: 892 pp.
17. Staheli LT, Hall JG, Jaffe KM, et al. Arthrogryposis: A text atlas. New York (1st ed). Location: Cambridge University Press 1998:158pp.

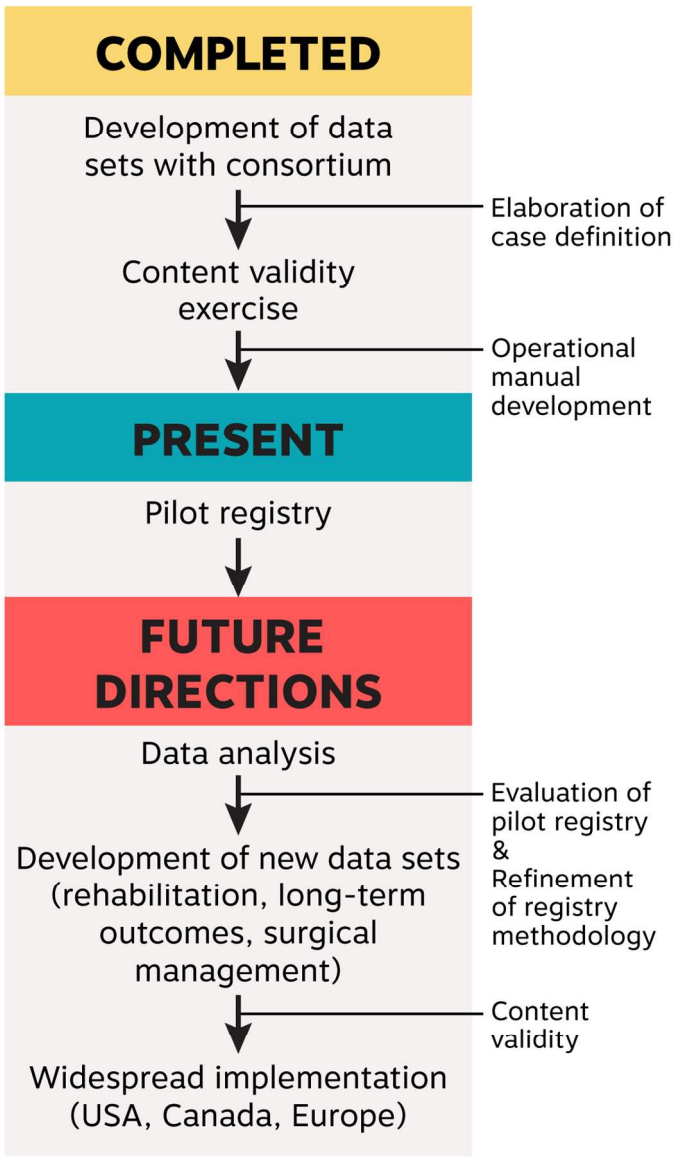

Figure 1. Timeline for the pilot registry and projection.

96x162mm (300 x 300 DPI)

CHILD	**Demographics**
	Race and ethnicity
	Medical history
	· Measurements at birth
	· Apgar scores
	· Complications at birth
	· Interventions at birth
	· Fractures at birth
	Clinical features
	· Facial abnormalities
	· Neurological abnormalities
	· Internal abnormalities
	· Skin or soft tissue abnormalities
	· Feeding
	· Metabolic disease
	· Contractures at birth
	· Interventions to correct bony deformities and/or joint contractures
	Prolonged hospitalization or re-admission
	Detection, diagnostic and referral history
MOTHER	**Sociocultural background**
	Lifestyle habits
	Medical history
	Labour and Delivery
FATHER	**Sociocultural background**
	Lifestyle habits
	Medical history

Figure 2. List of data sets for the pilot registry.

114x165mm (300 x 300 DPI)

BMJ Open

Development of a research platform for children with arthrogryposis multiplex congenita: Study protocol for a pilot registry.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-021377.R1
Article Type:	Protocol
Date Submitted by the Author:	04-May-2018
Complete List of Authors:	Dahan-Oliel, Noémi; Shriners Hospitals for Children Canada, Clinical research; McGill University, School of Physical and Occupational Therapy Bedard, Tanya; University of Calgary and Alberta Health Services Department of Paediatrics Darsaklis, Vasiliki Betty; Shriners Hospitals for Children Canada, Rehabilitation Hall, Judith; BC's Children's Hospital, Medical Genetics van Bosse, Harold; Shriners Hospitals for Children Philadelphia Hamdy, Reggie; Shriners Hospitals for Children Canada, Clinical research; McGill University, Faculty of Medicine, Department of Orthopedics
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Patient-centred medicine
Keywords:	Paediatric orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, STATISTICS & RESEARCH METHODS, Paediatric clinical genetics & dysmorphology < GENETICS, EPIDEMIOLOGY

Title page

Manuscript title:

Development of a research platform for children with arthrogryposis multiplex congenita: Study protocol for a pilot registry

Corresponding author:

Noémi Dahan-Oliel, PhD, OT

Clinical Research Department, Shriners Hospital for Children-Canada

1003 Decarie Boulevard

Montreal, Quebec H4A 0A9, Canada

Telephone: 514-842-4464 extension 2278

Fax: 514-842-7553

Email: ndahan@shrinenet.org

Authors' names and addresses:

Noémi Dahan-Oliel[1,2], Tanya Bedard[3], Vasiliki Betty Darsaklis[1], Judith Goslin Hall[4], Harold J.P. van Bosse[5], Reggie Charles Hamdy[1,6]

1. Shriners Hospital for Children, Montreal, Canada
   1003 Decarie Boulevard
   Montreal, Quebec H4A 0A9, Canada
2. School of Physical and Occupational Therapy, McGill University, Montreal, Canada
   3654 Promenade Sir-William-Osler
   Montreal, Quebec H3G 1Y5, Canada
3. Alberta Congenital Anomalies Surveillance System
   Alberta Children's Hospital
   288 Shaganappi Trail NW
   Calgary, AB T3B 6A8, Canada
4. Department of Medical Genetics and Department of Pediatrics,
   University of British Columbia and BC Children's Hospital,

Room C234

4500 Oak Street

Vancouver, BC V6H 3N1, Canada

5. Shriners Hospital for Children, Philadelphia, USA

3551 North Broad Street

Philadelphia, PA 19140, USA

6. Department of Pediatric Surgery

McGill University Health Centre

The Montreal Children's Hospital

1003, boulevard Décarie, Suite 6.59A

Montréal, Québec H4A 0A9, Canada

Word count: 2093

Development of a research platform for children with arthrogryposis multiplex congenita: Study protocol for a pilot registry

ABSTRACT

Introduction. Arthrogryposis multiplex congenita (AMC) describes a heterogeneous group of conditions with multiple congenital contractures. These conditions may be attributed to genetic or other factors inducing decreased fetal movements, including maternal and paternal factors. Discovering the underlying genetic pathways has important repercussions for prevention, gene therapy and genetic counseling. The current literature mainly consists of small-scale, single-site studies, limiting comparability and pooling of findings across individual studies. A pilot registry for children presenting with AMC is proposed to provide the framework for a large scale AMC registry. This registry will provide the platform to support high quality studies to inform the distribution, clinical practice and genetics contributing to this group of conditions. **Methods and analysis.** The registry will be piloted on 40 families of children from birth to 21 years of age presenting with AMC. Data will be collected on the child (demographic and newborn variables), mother and father (demographic, lifestyle habits and medical history). To promote standardized data collection, a manual of operations will be developed. Descriptive statistics will be used to summarize relevant data, regression analyses will be used to explore associations to generate hypotheses regarding factors contributing to AMC. Qualitative analysis will also be used to better describe the various phenotypes. **Ethics and dissemination.** Ethics approval was obtained at the participating sites. The pilot registry will provide the platform for multi-site AMC registry that will generate

multiple research avenues to enhance current care and establish new therapies. Following this pilot study, the participant selection criteria will be refined; data sets will be expanded to include rehabilitation and surgical interventions, and genetic sequencing; and the best timing for the questionnaire administration and frequency of follow-up prior to the implementation of a multi-site AMC registry will be determined.

Strengths & Limitations

- An international multidisciplinary team of experts contributed to the development of this registry.
- This is the first registry of its kind for AMC.
- Sustainability of any registry is dependent on funding.
- This registry will provide a platform to generate future studies on the distribution, causes, interventions and outcomes.

BACKGROUND AND RATIONALE

Arthrogryposis and arthrogryposis multiplex congenita (AMC) are descriptive terms, rather than specific diagnoses, used for a heterogeneous group of conditions with multiple congenital contractures and are often used interchangeably. This group of conditions affects 1 in 3000 live births[1,2] and result from a lack of fetal movement[3]. Individuals born with these conditions exhibit multiple joint contractures in at least two different body areas, including the upper and lower limbs, spine and jaw[1] as depicted in Figures 1-3. AMC may represent complex cases as impairments in other systems including gastro-intestinal, genito-urinary and central nervous systems are common.[4]

Hall,[5] recommended classifying cases using the following categories to aid in a specific diagnosis in AMC: i) limb involvement only, ii) limb with other system involvement, and iii) neuromuscular involvement with central nervous system dysfunction or intellectual disability. A specific diagnosis is based on the evaluation of pregnancy and delivery history, a detailed physical examination with documentation as to which joints are affected and the degree of extension and/or flexion, the examination of radiographs and photographs, and the natural history of complications in response to different interventions.[5] Laboratory tests, such as muscle biopsies, blood tests, and genetic analysis, also contribute to a specific diagnosis.

AMC may occur as part of inherited single-gene disorders or may occur sporadically. Currently, over 300 genes have been associated with AMC;[6,7] however, it is unclear how these mutations lead to the clinical presentation of AMC as less than half of patients have a mutation in one of the known AMC-related genes.[8] Discovering the genetic pathways responsible for these conditions have important repercussions for

prevention, gene therapy and genetic counseling. AMC may also be attributed to other factors inducing decreased fetal movements. These include maternal factors such as structural uterine anomalies that result in fetal crowding, exposure to teratogens, maternal conditions (such as myasthenia gravis and multiple sclerosis) and physical health status at time of conception and during gestation. Paternal influences may also play a key role and need to be studied further.[9,10] Factors integral to understanding the long-term needs of individuals with rare conditions, such as individuals presenting with AMC, relate to the distribution and natural history and are lacking in the literature. The terminology and definitions used by various disciplines to classify and describe this group of conditions and applied outcome measures are often inconsistent. The International Classification of Diseases (ICD), a standard diagnostic tool used in epidemiology, and health management does not provide the necessary details to easily retrieve cases presenting with AMC for research and clinical purposes, nor does it indicate severity or etiological information.

Research studies in AMC are often fragmented, isolated, and are small-scale. Conducting research in rare diseases poses several challenges. Investigator-initiated research often results in small sample sizes,[11] precluding the use of robust statistical methods and limiting the findings' external validity. Comparability and pooling of findings across individual studies in rare diseases often lack standardization in methodology and will vary in data collection, selection criteria, classification and outcome measures.[12] Currently, there is no comprehensive registry or classification system to support the high quality studies needed to inform the distribution, clinical practice and genetics contributing to this group of conditions. Multi-site collaborations across a breadth of disciplines offer enormous scientific leveraging opportunities. The

creation and implementation of a multi-site AMC registry will provide the opportunity to collaborate and develop standardized methodologies to contribute to rigorous research and enhance current care and establish new therapies. Prior to the full implementation of the AMC registry, a pilot registry will be developed.

Case definition

A clear and standardized case definition is necessary to ensure that all potential participants of the registry can be systematically and correctly identified and approached for recruitment. Considering the heterogeneity of the population presenting with AMC, as well as the lack of proper coding systems within healthcare institutions to properly denote individuals with a clinical presentation of AMC,[2] a specific case definition was developed through consultation with a panel of experts on AMC and registry development. This definition includes a description of clinical presentation, onset, factors associated with these conditions, as well as functional and long-term implications.

Data Elements

The final data set for the pilot registry was validated through the method proposed by Lawshe.[13,14] Content validation of any instrument is crucial prior to piloting its use to ensure that an instrument covers the universe of the content but is free of unwanted or irrelevant details for the overall purpose.[15] Validation of the data set is essential to ensure that the information collected will be pertinent to ultimate end users of the knowledge (clinicians, families, patients). The final data set only includes items with high content validity ratios, thereby increasing the efficiency and significance of the data elements for the AMC registry. The specifics of this method as well as the results of the exercise will be shared through future publications.

The **objectives** of the pilot registry for AMC are to:

- Provide the framework to fully implement the AMC registry
- Provide opportunities to refine participant selection criteria, and expand data sets to include rehabilitation, surgical management and genetic sequencing
- Determine the best timing of questionnaire administration and frequency of follow-up
- Resolve potential challenges before the full implementation of the AMC registry

METHODS

Study design

The pilot registry is a cross-sectional multicenter registry. Retrospective data from the time of pregnancy, birth, and neonatal period of the registered child will be collected for the pilot phase of this registry; the full AMC registry will consist of a prospective registry using both retrospective and cross-sectional data. This registry was initiated by a panel of experts, which identified the gaps in research and clinical therapies for children presenting with AMC. Included disciplines were: rehabilitation, genetics, orthopedics, clinical research and registry management. Additionally, patient representativeness was ensured through the inclusion of a patient advocate. Prior to full registry implementation, the registry will be pilot tested with 40 families. Pilot testing is crucial to determine the feasibility of a study prior to launching a large-scale multi-site project. It allows the investigators to solve potential issues prior to full expansion. Figure 4 represents the timeline for the pilot registry and its projection.

Patient and Public Involvement

Patient engagement has been intrinsic to the conception of the AMC registry. The initial panel of experts included the founder from a North American patient support group so that the youth and families' voices were considered from the start. During a knowledge exchange day geared towards families and individuals with AMC and the patient support group's annual meeting, it was identified that learning more about the genetics behind AMC, treatment effectiveness as well as long-term outcomes was a main priority. These issues are close to the hearts of those affected by AMC and are therefore integral to the registry. Additionally, content validation for the final data set included patient perspectives to ensure that their concerns were being addressed. Results of the pilot phase of the registry will be shared with families and youth with AMC via newsletters through accessible channels such as the website for the support group.

Study Setting

The AMC registry will be pilot tested at two Shriners Hospital for Children (SHC) sites: the SHC-Canada in Montreal, Quebec and SHC-Philadelphia. These two sites were purposefully selected as they have a relatively large, diverse population of patients presenting with AMC thus facilitating recruitment and providing the opportunity to explore contributory factors of these conditions for the pilot phase.

Eligibility Criteria, Sample Size and Recruitment Procedures

Families will be recruited based on having at least one child (0-21 years old) with the common clinical manifestation of multiple congenital contractures. Eligibility for the registry will be confirmed by the orthopedic surgeons who are treating at both sites (HVB and RH). Participants will be recruited during their outpatient clinic visit at each

respective site by the research assistant, who will provide information regarding the pilot registry and review the consent/assent forms as appropriate. A tentative appointment for the telephone interview will be scheduled. However, if preferred by the family, they will be re-contacted by e-mail to schedule an appointment. The primary caregiver from forty families, 20 from each site, will be required to complete the telephone interview with the research assistant. Some attrition is expected (completed consent but incomplete interview); however, as this registry is a pilot, the attrition rate cannot yet be estimated and will be calculated after the completion of this pilot study. Recruitment will therefore continue until all 40 interviews have been completed. Total sample size and attrition rate will then be calculated, and will be used to inform recruitment for the full multi-site AMC registry.

Data Collection Methods

The AMC pilot registry was modelled after the established Canadian Cerebral Palsy registry and tailored using the reference manual "Arthrogryposis: A Text Atlas".[16] This resulted in a manual of operations for a standardized data collection process and a comprehensive AMC-specific case report form (CRF) which includes the data elements for the pilot registry. These elements are listed in figure 5 and correspond to the child (e.g. date of birth, place of birth, birthweight and gestation, race and ethnicity, diagnoses), maternal and paternal demographics (date of birth, residence, ethnicity, lifestyle habits), pregnancy (antenatal conditions), and birth (delivery information), maternal and paternal medical history (preexisting conditions, prescription use).

Prior to piloting, a standardized training module will be completed by each research assistant to ensure that recruitment, data collection, and data entry are performed

in a consistent manner across both recruiting sites. Data will be collected from both the medical chart and the telephone interview, as using multiple sources to confirm the same data can minimize inadequacies found in one-source data. This data will be used to complete the CRF.

Data Management

The CRF will be used to populate OnCore, a secure electronic database used by the Shriners system. This common method of data entry facilitates easy access to the comprehensive inventory of information and enables sharing between facilities on secured servers.[17] A data monitoring committee is not assigned to this pilot registry as no adverse events are expected since no interventions will be administered to participants as part of this pilot registry. Data will be secured and password protected and only accessed by registry personnel at the Shriners Hospitals for Children.

Essential to standardized data collection will be manual of operations, which will include detailed data collection procedures, a data dictionary, documentation requirements, validation rules, and enhanced ICD-10 codes to ensure straightforward data retrieval.

Statistical Analysis

Descriptive statistics will be used to summarize relevant data. These will be reported as means, medians, and proportions with corresponding measures of error as deemed appropriate. Regression analyses will be used to explore associations to generate hypotheses regarding risk factors, interventions and outcome, which will be further explored in the multi-site AMC registry. Qualitative analysis will also be used to describe the various phenotypes of AMC conditions. Additionally, the information collected from

the two sources (i.e., telephone interview and medical chart) will be checked for completeness. If a discrepancy between the two sources is identified, two researchers (NDO and TB) will select the data source to be used based on the variable collected. Additional sources of information often give more insight into a topic, and multiple sources provide verification and validity while complementing similar data. The data source (i.e., telephone interview and medical chart) will therefore be determined a priori based on this comparison.[18] By targeting medical chart requisitions, data collection will be facilitated in the larger scale implementation.

Closure of Pilot Registry

The pilot phase of the AMC registry will end once 40 families have completed the telephone interview. Recruitment procedures will be evaluated and preliminary data analyses will be completed. Expansions to the registry content as well as to participating sites will be reviewed with the panel of experts.

ETHICS

Research Ethics Approval and Protocol Amendments

Research ethics and administrative site approvals have been received at both the SHC-Canada and SHC-Philadelphia sites. Since the registry is not a clinical trial, this protocol was not been registered. Administrative site approval was obtained from the Department of Medical Research at Shriners Hospitals for Children Sponsor (CAN1711). Research ethics approval was obtained from the McGill University Faculty of Medicine

Institutional Review Board (A00-M34-17A) for SHC-Canada and from the Western Institutional Review Board (1182229) for SHC-Philadelphia. Minor wording revisions were required to the consent and assent forms prior to obtaining final ethics approval. The protocol was accepted as submitted.

Consent/Assent

Patient participation is completely voluntary, and informed written consent will be obtained prior to participation. This consent will be obtained while the patients are present for AMC clinic by the research assistant 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 7-14. For patients older than 14 years of age, consent will be obtained from both the parent and the child to ensure participation. In the United States site, children between the ages of 7-17 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.

Confidentiality and Access to Data

OnCore is used in all SHC studies for the management of clinical research data. This secure database implements industry best practices and ongoing monitoring activities, such as daily-encrypted backups of hosted customer data. Only authorized personnel will have access to the CRF, which will be stored in a locked file cabinet. Specific individual information in the registry will not be shared with other persons, entities or companies unless obligated by legal authorities. Data collection will be performed locally and anonymized in the online OnCore Enterprise Research software.

Dissemination Policy

Results from the pilot phase of the registry will be shared through a manuscript regarding the findings of this study. Additionally, information briefs will be provided to the participating clinicians and families. These information briefs will contain the most pertinent findings from the pilot phase as well as future directions for research, specifically for the full multi-site registry. A summary of the research findings will also be made available to the sponsor of the study. Authorship will be based on the following criteria: substantial contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of data.

DISCUSSION

The pilot AMC registry is designed to provide the platform for the generation of hypothesis-driven multi-center longitudinal studies in AMC. To date, little is known about these conditions with respect to etiology and natural history. Evidence and effectiveness of various therapies (genetic, surgical and rehabilitative) are lacking. Considering the relative rarity and heterogeneity of AMC, large sample sizes to conduct research with generalizable outcomes is nearly impossible to gleam from single-site studies. Multi-site collaboration is warranted and can be achieved through a registry. A standard case definition is essential to ensure that all potential participants are consistently recruited across sites so that the sample size can be as large as possible. A comprehensive CRF is essential to ascertain all salient information required for future research avenues. The creation of a manual of operations will facilitate the implementation of an AMC registry by providing standardization regarding data

collection procedures as well as definitions and enhanced ICD-10 codes to be used for cases with different types of AMC. The generation of an online database that can be shared between sites will facilitate data collection, data entry, and analysis.

The novelty of this approach with this population, requires a pilot phase of the AMC registry to test feasibility (including need for personnel training) and impact on families. Piloting the registry on 40 participants across two SHC sites will provide important information with respect to ease of recruitment, length of administration, and ease of execution. Random audits on 20% of the data registry (4 at each site) will contribute to data quality assurance.

SUMMARY

Establishing a pilot AMC registry will provide the platform for a full expansion of the AMC registry to generate multiple research avenues to enhance current care and establish new therapies. Following this pilot study, we will refine the participant selection criteria and determine the best timing for the questionnaire administration and frequency of follow-up. As AMC includes a group of rare conditions, this protocol will also serve to guide the establishment of future rare disease registries.

Figure Legends

Figure 1a and b. Spinal deformities of varying severity.

Figure 2. Images depicting upper limb involvement, a. thumb-in-palm and overlapping fingers, b. flexion contracture at the elbows and wrists, and absence of skin creases at the elbow, c. internal rotation with extension contracture at the elbow.

Figure 3. Images depicting lower limb involvement, a. clubfeet, b. flexion contracture of the knee and webbing in the popliteal region, c. flexion contracture at the hips.

Figure 4. Timeline for the pilot registry and projection.

Figure 5. List of data sets for the pilot registry

Author's contributions

NDO, RH, TB, HvB, and JH initiated and planned this study as well as developed all associated materials. **NDO, TB, VD** wrote the protocol and the paper**. NDO, RH, TB, HvB, JH** obtained funding. All authors read and approved the final version of this paper. **NDO, RH and HVB** will conduct the pilot phase of the registry.

Funding

The development of the data sets, content validity and pilot phases are funded by a Developmental Clinical Grant from the Shriners Hospitals for Children grant number 79150. The planning activities and face-to-face meeting for the panel of experts were funded by a planning and dissemination grant from the Canadian Institutes of Health Research – Institute of Musculoskeletal Health and Arthritis grant number 144020.

Competing interests

The authors report no competing interests.

Acknowledgments

The authors acknowledge the administrative support of Carla Evangeliste and Nicole Young, graphic and medical illustrations by Guylaine Bédard and Denis Alves, and the scientific, clinical and expert contributions of Dr. Bonita Sawatzky, Ani Samargian, Kathleen Montpetit, Caroline Elfassy, Rita Yap, Emily Lecker, Dr. Maryam Oskoui, and Dr. Michael Shevell. We would also like to thank the families and patients who

participated in the various patient engagement activities and who contributed to the final data set development.

References

1. Hall JG. Arthrogryposis multiplex congenita: etiology, genetics, classification, diagnostic approach, and general aspects. *J Pediatr Orthop B* 1997 Jul;6(3):159-66.
2. Lowry RB, Sibbald B, Bedard T, et al. Prevalence of multiple congenital contractures including arthrogryposis multiplex congenita in Alberta, Canada, and a strategy for classification and coding. *Birth Defects Res A Clin Mol Teratol* 2010 Dec;88(12):1057-61. doi: 10.1002/bdra.20738. [Published online First: 15 November 2010].
3. Bevan WP, Hall JG, Bamshad M, et al. Arthrogryposis multiplex congenita (amyoplasia): an orthopaedic perspective. *J Pediatr Orthop* 2007 Jul-Aug;27(5):594-600.
4. Bernstein RM. Arthrogryposis and Amyoplasia. *J Am Acad Orthop Surg* 2002 Nov-Dec;10(6):417-24
5. Hall JG. Arthrogryposis (multiple congenital contractures): Diagnostic approach to etiology, classification, genetics, and general principles. *Eur J Med Genet* 2014 Aug;57(8):464-72 doi: 10.1016/j.ejmg.2014.03.008 [Published online First: 3 Apr 2014].
6. Hall JG. Genetic aspects of arthrogryposis. *Clin Orthop Relat Res* 1985 Apr;(194):44-53.
7. Hunter JM, Kiefer J, Balak CD, et al. Review of X-linked syndromes with arthrogryposis or early contractures-aid to diagnosis and pathway identification.

Am J Med Genet A 2015 May;167A(5):931-73 doi: 10.1002/ajmg.a.36934 [Published online First: 19 March 2015].

8. Bamshad M, Van Heest AE, Pleasure D. Arthrogryposis: a review and update. *J Bone Joint Surg Am* 2009 Jul;91(Suppl 4):40-6 doi: 10.2106/JBJS.I.00281
9. Reddihough DS, Collins KJ. The epidemiology and causes of cerebral palsy. *Aust J Physiother* 2003;49(1):7-12.
10. Feinberg JI, Bakulski KM, Jaffe AE, et al. Paternal sperm DNA methylation associated with early signs of autism risk in an autism-enriched cohort. *International Journal of Epidemiology* 2015 44(4)1199–1210 https://doi.org/10.1093/ije/dyv028 [Published online First: 1 August 2015]
11. Augustine EF, Adams HR, Mink JW. Clinical trials in rare disease: challenges and opportunities. *J Child Neurol* 2013 Sep;28(9):1142-50 doi: 10.1177/0883073813495959
12. Griggs RC, Batshaw M, Dunkle M, et al. Clinical research for rare disease: Opportunities, challenges, and solutions. *Mol Genet Metab* 2009 Jan;96(1):20-6 doi: 10.1016/j.ymgme.2008.10.003. [Published online First: 13 November 2008]
13. Lawshe CH. A Quantitative Approach to Content Validity. *Personnel Psychol* 1975;28(4):563–75 doi: 10.1111/j.1744-6570.1975.tb01393 [Published online: 7 December 2006]
14. Wilson FR, Pan W, Schumsky DA. Recalculation of the critical values for Lawshe's content validity ratio. *Measurement and Evaluation in Counseling and*

Development 2012 45(3), 197-210 doi:10.1177/0748175612440286. [Published online: 10 Mar 2017]

15. Portney LG, Watkins MP. Foundations of clinical research: Applications to practice (3rd ed.). Upper Saddle River, NJ: Pearson & Prentice Hall 2009: 892 pp.
16. Staheli LT, Hall JG, Jaffe KM, et al. Arthrogryposis: A text atlas. New York (1st ed). Location: Cambridge University Press 1998:158pp.
17. Gliklich R, Dreyer N, Leavy M, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. Two volumes. (Prepared by the Outcome DEcIDE Center [Outcome Sciences, Inc., a Quintiles company] under Contract No. 290 2005 00351 TO7.) AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. http://www.effectivehealthcare.ahrq.gov/registries-guide-3.cfm. (accessed 15 December 2017)
18. Mant J, Murphy M, Rose P, Vessey M. The accuracy of general practitioner records of smoking and alcohol use: comparison with patient questionnaires. *J Public Health Med* 2000 22(2):198-201.

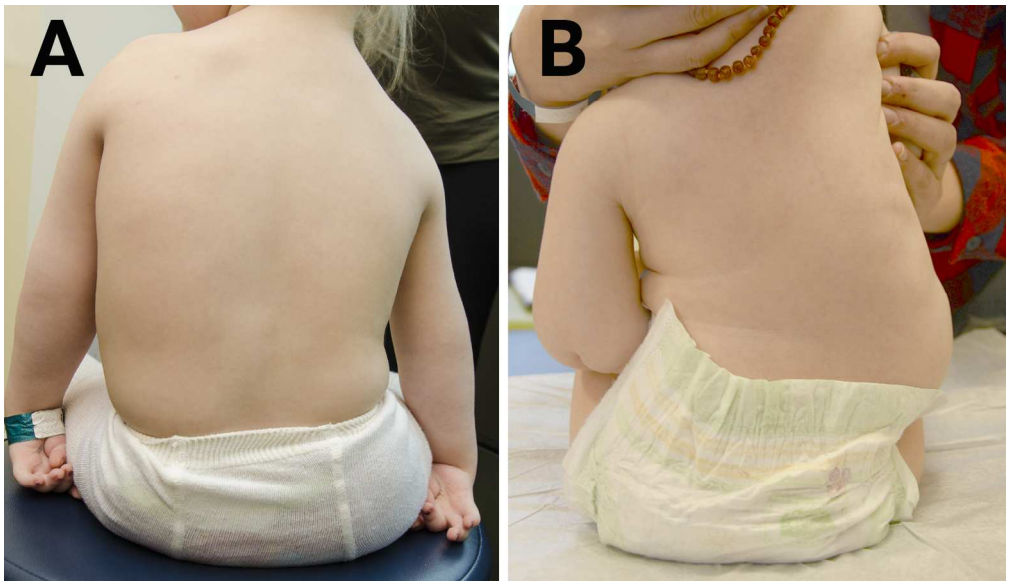

Figure 1a and b. Spinal deformities of varying severity.

177x102mm (300 x 300 DPI)

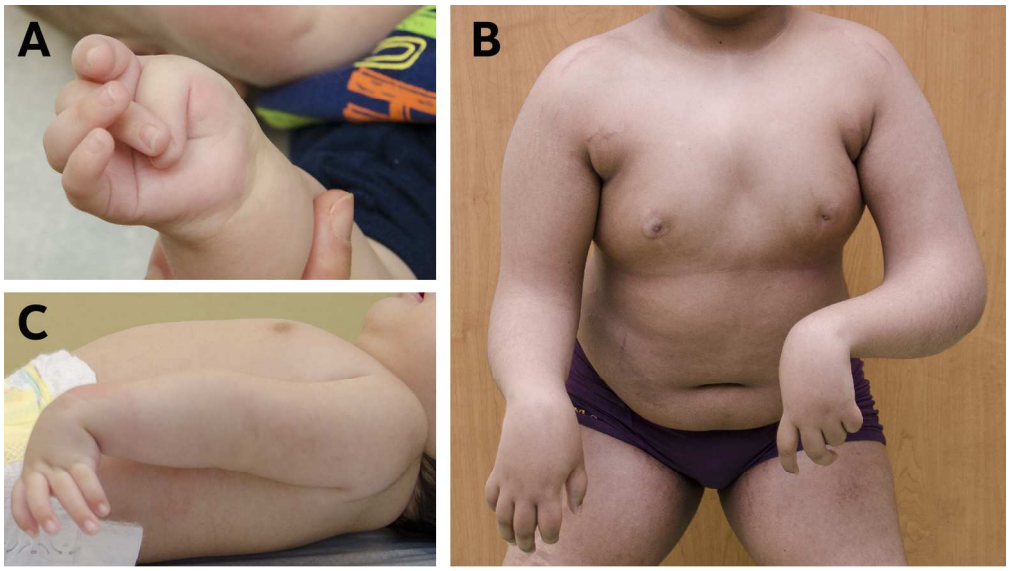

Figure 2. Images depicting upper limb involvement, a. thumb-in-palm and overlapping fingers, b. flexion contracture at the elbows and wrists, and absence of skin creases at the elbow, c. internal rotation with extension contracture at the elbow.

177x99mm (300 x 300 DPI)

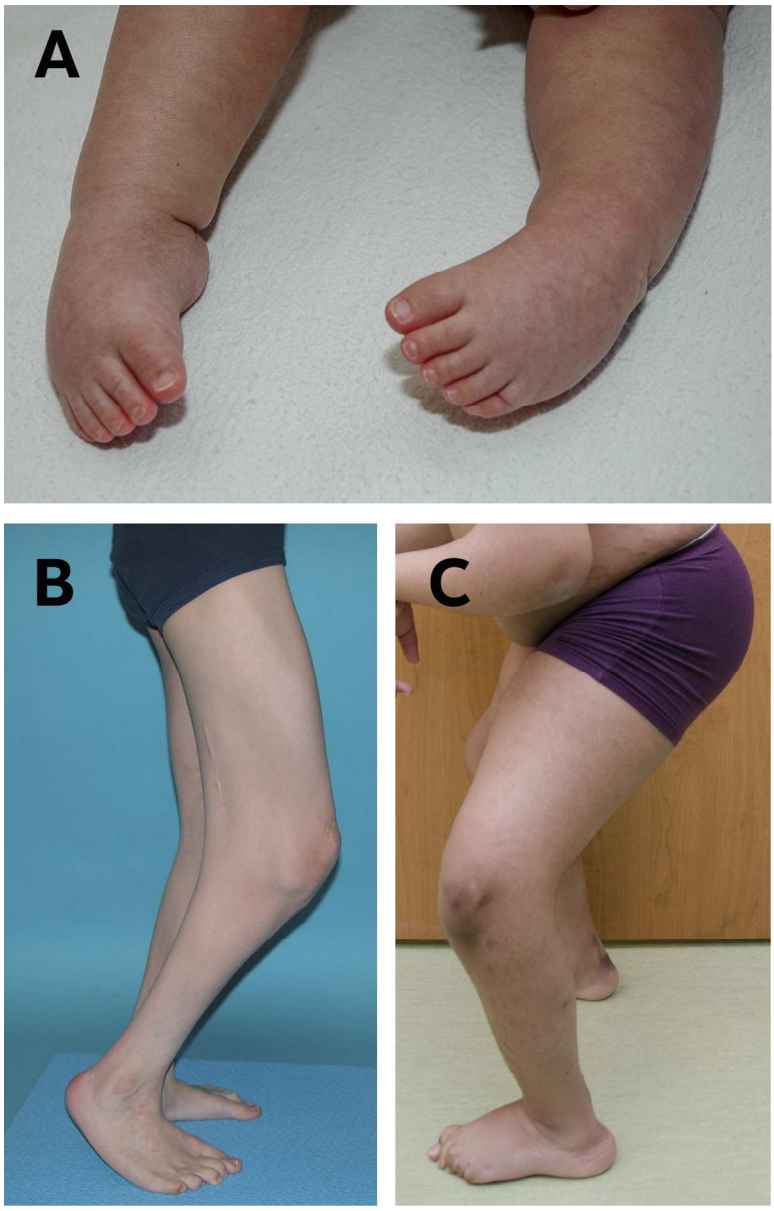

Figure 3. Images depicting lower limb involvement, a. club feet, b. flexion contracture of the knee and webbing in the popliteal region, c. flexion contracture at the hips.

113x177mm (300 x 300 DPI)

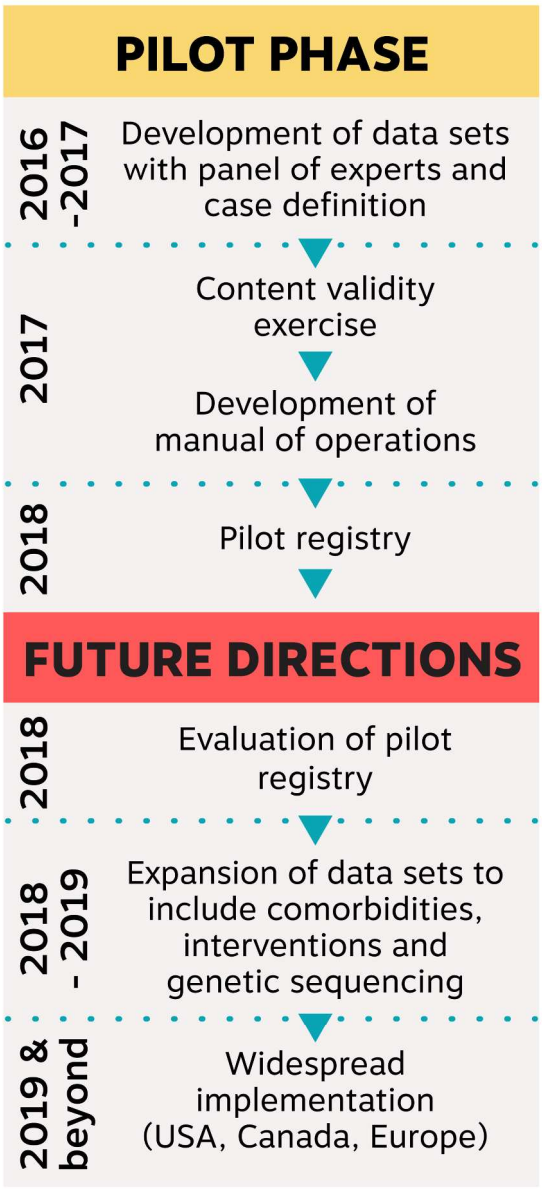

Figure 4. Timeline for the pilot registry and projection.

126x273mm (300 x 300 DPI)

CHILD	**Demographics**
	Race and ethnicity
	Medical history
	· Measurements at birth
	· Apgar scores
	· Complications at birth
	· Interventions at birth
	· Fractures at birth
	Clinical features
	· Facial abnormalities
	· Neurological abnormalities
	· Internal abnormalities
	· Skin or soft tissue abnormalities
	· Feeding
	· Metabolic disease
	· Contractures at birth
	· Interventions to correct bony deformities and/or joint contractures
	Prolonged hospitalization or re-admission
	Detection, diagnostic and referral history
MOTHER	**Sociocultural background**
	Lifestyle habits
	Medical history
	Labour and Delivery
FATHER	**Sociocultural background**
	Lifestyle habits
	Medical history

Figure 5. List of data sets for the pilot registry.

114x165mm (300 x 300 DPI)