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Published in:
BMJ Open

DOI:
10.1136/bmjopen-2018-022190

Publication date:
2018

Document version
Publisher's PDF, also known as Version of record

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Citation for published version (APA):

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Comprehensive investigation of congenital anomalies in cerebral palsy: protocol for a European-Australian population-based data linkage study (The Comprehensive CA-CP Study)

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ABSTRACT

Introduction Cerebral palsy (CP), an umbrella term for non-progressive conditions of cerebral origin resulting in motor impairments, is collectively the most common cause of physical disability in childhood. Cerebral and/or non-cerebral congenital anomalies are present in 15%–40% of children with CP. In order to identify effective prevention strategies for this substantial proportion of CP, a comprehensive understanding of the epidemiology of these congenital anomalies is required. International collaboration is needed, as previous attempts have fallen short due to a lack of power, since the anomalies are individually rare and CP comprises many clinical descriptions. The aim of this study is to generate new knowledge about the aetiologies of CP through a focused investigation into the role of congenital anomalies.

Methods and analysis This collaborative, population-based data linkage study includes nine geographic regions (six in Europe, three in Australia) served by both congenital anomaly and cerebral palsy (CP) registers. The integrity of the collaborative study will be maintained by the use of strict definitions of CP and included congenital anomalies, as well as flexibility in the inclusion of registers in individual analyses. By obtaining congenital anomaly data from both CP and congenital anomaly registers, this study enables access to the most comprehensive and highest quality description of congenital anomalies. This study will be the first to report risk of CP for individuals with the congenital anomalies most strongly associated with CP. A limitation of the study is the possibility of migration of children with congenital anomalies out of a region, prior to a description of CP at age 4 or 5 years, which may lead to underestimation of cases with both CP and congenital anomalies.

INTRODUCTION

Cerebral palsy (CP) is an umbrella term for non-progressive motor impairment conditions secondary to lesions or malformations of the developing brain. The condition is also associated with impairments of cognition, sensation and/or epilepsy.1 Known risk factors for this lifelong disability span the period prior to conception through to 2 years of age.1 They include genetic factors, multiple births, congenital anomalies, intrauterine growth restriction, infection, preterm birth and hypoxia ischaemia, as well as events in early childhood such as cerebrovascular accidents.1 After a relatively stable birth prevalence of 2–2.5/1000 live births over the last

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Received 7 February 2018
Revised 17 May 2018
Accepted 7 June 2018

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60 years, the most recent evidence from Europe and Australia suggests we are starting to see a decline.\textsuperscript{1–3} It is anticipated that these declines are in children born very preterm and those with hypoxic ischaemia at birth where neonatal interventions have proven effective.\textsuperscript{3}

The prevalence of congenital anomalies is estimated at approximately 3\%–6\% of the population,\textsuperscript{4,5} depending on how both congenital anomalies and the denominator are defined. Congenital anomalies can occur in any body system as an isolated anomaly or as multiple anomalies and range from minor to severe or lethal. Recognised aetiologies are heterogeneous, and include chromosomal and genetic abnormalities, teratogenic exposure, micronutrient deficiencies and infectious disease but a large proportion have no recognised aetiology, further complicating epidemiological studies.\textsuperscript{6} Congenital anomalies can result in lifelong morbidity and disability, and are responsible for 276,000 neonatal deaths worldwide annually.\textsuperscript{7}

Register-based studies have determined that congenital anomalies occur more frequently in children with CP than the general population.\textsuperscript{8–10} European and Australian register-based studies have described anomalies in 15\%–40\% of children with CP.\textsuperscript{10,11} The increased risk of anomalies exists for those with a presumed pre/perinatal brain injury, as well as those with a recognised postneonatal cause.\textsuperscript{12} An increased rate both of cerebral and of non-cerebral anomalies, particularly cardiac defects, has been described in the CP group.\textsuperscript{10,12–14} When congenital anomalies are observed in children with CP, they are often associated with more severe long-term outcomes.\textsuperscript{8–10,12}

Research in this area to date has considered individual registers or small linkage studies. Given the relatively rare occurrence of CP, and the vast range of possible congenital anomalies, much larger study samples are required to generate statistically robust observations. With a larger population, research can focus on investigating groups of cases with similar anomalies and exploring their aetiology and outcomes.

No previous study has been able to determine the risk of CP for children born with specific congenital anomalies. This is important information both for clinicians prognosticating to families and to raise awareness among researchers who are working on the prevention of malformations that they may also prevent some cases of cerebral palsy. We seek to redress this gap in our study.

To devise an appropriate and feasible collaboration, we distributed a survey to all known CP and congenital anomaly registers in Europe and Australia. The survey aimed to elucidate inclusion/exclusion criteria, methods of data collection and data available at each register and to ascertain their interest in participating in this collaboration. The results of the survey have helped to shape the scope and design of this study protocol. Of the 47 registers contacted, 37 responded (79\% response rate): 26 European and 11 Australian. The definitions used for CP were consistent; however, inclusion/exclusion criteria for congenital anomalies differed. The coding of anomalies differed by type of register and geographical region, and even within individual registers over time; however, these variations can be addressed using conversion codes and a computer algorithm. This process identified populations served by both a CP register and a congenital anomaly register who were willing and able to collaborate from four European and two Australian regions; unfortunately, one European CP register has since unexpectedly closed necessitating withdrawal from the study. Further discussions with non-responders to the survey resulted in an additional three regions from Europe and one region from Australia joining the study. More than 270,000 live births/year occur within these nine regions, and this study will therefore consider approximately seven times the sample size of the largest previous equivalent study (table 1).\textsuperscript{10} The Comprehensive CA-CP Study will pool data from registers in the Surveillance of Cerebral Palsy in Europe (SCPE) and in the European Surveillance of Congenital Anomalies (EUROCAT) with that from the Australian Cerebral Palsy Register (ACPR) and Australian congenital anomaly registers.

METHODS AND ANALYSIS

Aim and research questions

The aim of The Comprehensive CA-CP Study is to generate new knowledge about the aetiologies of CP through a focused investigation into the role of congenital anomalies in the mechanisms leading to CP. Our research questions are: (a) What is the frequency and proportion of children with CP (described by gestational age groupings, sex and plurality) that have recognised cerebral and/or non-cerebral congenital anomalies?; (b) What are the clinical outcomes (including motor type, gross motor severity and associated impairments of intellect, vision, hearing, speech and epilepsy) of children with CP and specific congenital anomalies, compared with children with CP without anomalies?; (c) For infants with specific congenital anomalies, what is the associated risk of CP?; (d) Can the timing of congenital anomaly development and the timing of brain injury be identified and compared?; (e) Which anomalies are on a causal path to CP? Which of these have opportunities for primary and secondary prevention?

Design and setting

This data linkage study will consider European and Australian total populations of live births. CP and congenital anomaly register data from each participating region will be linked and subsequently pooled (table 1). A multidisciplinary approach is being used with individual collaborators from three register networks (EUROCAT, SCPE, ACPR) bringing expertise and experience from the fields of epidemiology, paediatrics, neonatology, neurology, genetics, public and allied health. EUROCAT is a European network of population-based registries for the epidemiological surveillance of congenital anomalies. The surveillance of congenital anomalies...
serves two main purposes: to facilitate the identification of teratogenic (malformation causing) exposures and to assess the impact of primary prevention and prenatal screening policy and practice at a population level.

Commencing in 1979, EUROCAT surveys more than 1.7 million births per year in Europe, involving 43 registries across 23 countries. The central database includes more than 340,000 European cases with major congenital anomalies. The contributing registries all use the same methods and are based on multiple data sources.

The SCPE network is a collaboration of clinicians and researchers working with population-based surveys or registers of children with CP and extending across Europe, currently with 24 partners in 20 countries. SCPE was established in 1998 to monitor trends in CP (the database comprises birth years 1975 onwards), to provide a framework for collaborative research, to serve as a basis for service planning and to raise standards of assessment and care for children with CP. The collaboration is examining variations in clinical practice and access to healthcare across Europe and further refining how children with CP are described, notably using neonatal neuroimaging classification. The participating registries use the same definition and classification of CP, and contribute data with the same coding.

The ACPR was established in 2008 and is a collaboration between the eight geographically defined CP registers that together represent all of Australia. It is a research database holding deidentified data contributed from each register, who share a common minimum data set.

**Participants**

To identify the congenital anomalies that co-occur in children with CP and their clinical outcomes (all research questions), participants will consist of all children with confirmed CP (verified at age 4 or 5 years) or with a description of CP after age 2 but without verification in the event of death prior to 4 or 5 years of age, both with and without congenital anomalies, born between 1991 and 2009 to mothers residing at birth in a region (or

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Table 1 Participating registers

<table>
<thead>
<tr>
<th>Geographical region</th>
<th>Cerebral palsy (CP) register</th>
<th>Congenital anomaly register</th>
<th>Live births/year</th>
<th>Birth years available</th>
<th>Total live births</th>
<th>Approximate CP cases available*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EUROPE†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funen, Denmark</td>
<td>Danish CP Register</td>
<td>EUROCAT Malformation Registry for Funen, Denmark</td>
<td>5000</td>
<td>1991–2007</td>
<td>85 000</td>
<td>179</td>
</tr>
<tr>
<td>Grenoble, France</td>
<td>RHEOP</td>
<td>REMERA</td>
<td>31 300</td>
<td>1991–2007</td>
<td>532 100</td>
<td>1117</td>
</tr>
<tr>
<td>Norway</td>
<td>The CP Register of Norway (CPRN)</td>
<td>Medical Birth Registry of Norway (MFR)</td>
<td>60 000</td>
<td>1999–2009</td>
<td>660 000</td>
<td>1386</td>
</tr>
<tr>
<td>Portugal</td>
<td>Programa Vigilância Nacional da Paralisia Cerebral aos cinco anos de Idade (PVNPC5A)</td>
<td>RENAC—Registro Nacional de Anomalías Congénitas</td>
<td>18 000</td>
<td>2001–2009</td>
<td>162 000</td>
<td>340</td>
</tr>
<tr>
<td>Western Sweden**</td>
<td>The CP Register of Western Sweden</td>
<td>Swedish Register of Birth Defects</td>
<td>24 000</td>
<td>1991–2009</td>
<td>408 000</td>
<td>857</td>
</tr>
<tr>
<td>Croatia</td>
<td>Register of Cerebral Palsy of Croatia (RCP-HR)</td>
<td>Zagreb EUROCAT Register</td>
<td>7000</td>
<td>2003–2007</td>
<td>35 000</td>
<td>74</td>
</tr>
<tr>
<td><strong>AUSTRALIA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Australia</td>
<td>South Australian Birth Defects Register‡</td>
<td></td>
<td>20 000</td>
<td>1993–2009</td>
<td>340 000</td>
<td>714</td>
</tr>
<tr>
<td>Victoria</td>
<td>Victorian Cerebral Palsy Register</td>
<td>Victorian Congenital Anomalies Register</td>
<td>70 000</td>
<td>1993–2009</td>
<td>1 104 389</td>
<td>2048</td>
</tr>
<tr>
<td>Western Australia</td>
<td>Western Australian Register of Developmental Anomalies (WARDA)‡</td>
<td></td>
<td>30 000</td>
<td>1991–2009</td>
<td>570 000</td>
<td>1197</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>265 300</td>
<td></td>
<td>3 896 489</td>
<td>7 912</td>
</tr>
</tbody>
</table>

*Calculated at 2.1/1000 live births.
†All participating European congenital anomaly registers follow EUROCAT methods.
**Individual case data cannot be contributed to the pooled data set housed in Australia. Tabulated data to be included during data analysis phase.
‡Colocated/combined congenital anomalies and CP register.
from two European studies.8 10 Anomalies associated in this population sample were compared with findings
d\lies to be considered (box CP across both regions comprise the final list of anoma-
larities, lesion or abnormality, and (5) the interference, lesion or abnormality that originates in the immature
brain.16

To ascertain the risk of CP for infants with specific congenital anomalies (research question c), participants
will constitute all live births with a confirmed diagnosis of the specific congenital anomaly (box 1), with or without
CP, born between 1991 and 2009 to mothers residing at birth in a region (or if not available, infants born in a
region) with a participating CP and congenital anomaly register in Europe or Australia.

The definition of a congenital anomaly varies widely, even between registers within one country.16 We have
identified that variations exist across registers with regards to which anomalies are routinely collected and
which anomalies are reliably identified by a certain age. Some congenital anomalies, such as brain malformations,
may not be identified in the neonatal period. Because of this, registers must accept notifications for at least 1 year
post birth to be included in these analyses. For anomalies readily identifiable in the neonatal period (eg, cleft lip
and palate), all registers will be included.

In order to identify which anomalies should be considered in research question c (risk of CP for specific congenital
anomalies) in this study, we analysed data from a large case–control study in Western Australia incorporating
data from the statewide CP and congenital anomaly registries.9 Congenital anomalies strongly associated with CP
in this population sample were compared with findings from two European studies.8 10 Anomalies associated with
CP across both regions comprise the final list of anomalies to be considered (box 1).

### Data linkage and harmonisation

Data linkage will take place locally by that region’s CP and congenital anomaly registers. Each region will nominate
their primary and secondary register for the study. Given the focus of the study and preliminary planning with
registers, the primary register will most often be the CP register. The linkage will commence with the secondary
register (likely to be the congenital anomaly register) providing a file of all registered congenital anomaly
cases born alive (1991–2009). The linkage process will be specific to each geographic region (eg, personal identifier
number, birth date, sex and/or delivery place), according to the data held by each register. The corresponding
CP register will check which of these children are also known to them. Each register will then add relevant data
for identified cases. Alternate methods of linkage will be used for those regions where (1) an internal linkage of
cases is feasible as the CP and congenital anomaly registers are colocated within the same register (two regions),
or (2) an independent data linkage service is used to link data from the two registers (one region). Finally, the
linked file with identifying information replaced with a

---

**Box 1  Congenital anomalies to be studied in research question c**

<table>
<thead>
<tr>
<th>Congenital anomaly (International Classification of Diseases, 10th Revision code and text description)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q040: Anomaly/agenesis corpus callosum</td>
</tr>
<tr>
<td>Q0433: Lissencephaly</td>
</tr>
<tr>
<td>Q042: Holoprosencephaly</td>
</tr>
<tr>
<td>Q031: Hydrocephalus and Dandy-Walker</td>
</tr>
<tr>
<td>Severe congenital heart defects according to European Surveillance of Congenital Anomalies definition:</td>
</tr>
<tr>
<td>Q200: Common arterial trunk</td>
</tr>
<tr>
<td>Q201: Double outlet right ventricle</td>
</tr>
<tr>
<td>Q203: Discordant ventriculoarterial connection</td>
</tr>
<tr>
<td>Q204: Double inlet ventricle</td>
</tr>
<tr>
<td>Q212: Atrioventricular septal defect</td>
</tr>
<tr>
<td>Q213: Tetralogy of Fallot</td>
</tr>
<tr>
<td>Q220: Pulmonary valve atresia</td>
</tr>
<tr>
<td>Q224: Congenital tricuspid stenosis</td>
</tr>
<tr>
<td>Q225: Ebstein anomaly</td>
</tr>
<tr>
<td>Q226: Hypoplastic right heart syndrome</td>
</tr>
<tr>
<td>Q230: Congenital stenosis of aortic valve</td>
</tr>
<tr>
<td>Q232: Congenital mitral stenosis</td>
</tr>
<tr>
<td>Q233: Congenital mitral insufficiency</td>
</tr>
<tr>
<td>Q234: Hypoplastic left heart syndrome</td>
</tr>
<tr>
<td>Q251: Coarctation of aorta</td>
</tr>
<tr>
<td>Q252: Atresia of aorta</td>
</tr>
<tr>
<td>Q262: Total anomalous pulmonary venous connection</td>
</tr>
<tr>
<td>Q203: Transposition of great arteries</td>
</tr>
<tr>
<td>Q234: Hypoplastic left heart</td>
</tr>
<tr>
<td>Q35: Cleft palate</td>
</tr>
<tr>
<td>Q35: Cleft lip with or without cleft palate</td>
</tr>
<tr>
<td>Q36: Cleft lip</td>
</tr>
<tr>
<td>Q37: Cleft palate with cleft lip</td>
</tr>
<tr>
<td>Q390: Atresia of oesophagus without fistula</td>
</tr>
<tr>
<td>Q391: Atresia of oesophagus with tracheo-oesophageal fistula</td>
</tr>
<tr>
<td>Q790: Diaphragmatic hernia</td>
</tr>
<tr>
<td>Q793: Gastrochisis</td>
</tr>
<tr>
<td>Q642: Posterior urethral valves</td>
</tr>
<tr>
<td>Q660: Clubfoot/talipes equinovarus</td>
</tr>
<tr>
<td>Q750: (Non-genetic) craniosynostosis</td>
</tr>
<tr>
<td>Eye anomalies:</td>
</tr>
<tr>
<td>Q110: Cystic eyeball</td>
</tr>
<tr>
<td>Q111: Other anophthalmos</td>
</tr>
<tr>
<td>Q112: Microphthalmos</td>
</tr>
<tr>
<td>Q120: Congenital cataract</td>
</tr>
<tr>
<td>Q150: Congenital glaucoma</td>
</tr>
<tr>
<td>Q53: Undescended testicle (Australian registers only)</td>
</tr>
</tbody>
</table>
null
of CP. Sample size calculations were completed using SPSS Sample Power 3 and show that our expected population exceeds the sample size estimated to be required for our research questions. Specific examples follow:

► Research question a ‘what is the frequency and proportion of children with CP that have a congenital anomaly?’ Given that approximately 5% of the general population have a congenital anomaly, at 90% power, a sample size of 13–90 cases of CP is required to detect a proportion of 15%–40% of CP cases having a congenital anomaly.

► Research question a stratified by GA ‘what is the frequency and proportion of children with CP that have a congenital anomaly, for term infants?’ 60% of children with CP are born at term, and the association with congenital anomalies is strongest in term infants. With 90% power, a sample size of 9–23 cases of CP is required to detect the proportion of term children with CP having a congenital anomaly.

► Research question c ‘what is the risk of CP for infants with specific congenital anomalies, for example holoprosencephaly?’ The least common targeted congenital anomaly for these analyses is holoprosencephaly. Literature suggests that 0.18% of CP cases have holoprosencephaly while the general population estimate is 0.24/10 000 live births. A sample size of 14 cases with holoprosencephaly in the general population is required to determine the risk of CP. We expect to have approximately 70 cases of this specific anomaly.

IBM SPSS V.24 will be used for statistical analysis for this research programme. After the data set from each region is received by the Cerebral Palsy Alliance, The University of Sydney, it will be analysed for missing data prior to pooling into one single file. Where a region has >20% of data missing for a variable, this variable will likely be excluded from that region’s final data set. However, if available data for that variable show the same trend as regions with minimal missing data, it may be included. This will be evaluated on a variable by variable basis. Data analyses will include: descriptive analyses of cerebral and non-cerebral anomalies found in CP; descriptive analyses of clinical outcomes (eg, type of CP, severity, additional non-motor impairments); descriptive analyses to compare timing of congenital anomaly and timing of brain injury/abnormality responsible for CP; ORs (univariate and multivariate) to calculate the odds of CP associated with specific congenital anomalies.

Patient and public involvement
The development of this research study protocol was informed by the responses of people with CP and their families to our Delphi study regarding research priorities for CP.24 A parent representative reviewed and contributed to a funding application for the study. The study plan was reviewed and approved by a consumer advisory committee from the Western Australian Register of Developmental Anomalies, which will contribute data to the study. Summaries of study results will be developed in consultation with consumer representatives from CP Quest and will be distributed through the newsletters of participating registers.

ETHICS AND DISSEMINATION
This overarching project has ethical approval. Furthermore, where an individual register deemed it necessary, additional ethical approval or permission to perform data linkages has been obtained. This study will result in the creation of a large data set, which will be used for

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**Figure 1** Quality assurance flowchart for resolving discrepancies between cerebral palsy (CP) and congenital anomaly registers. ICD, International Classification of Diseases.
multiple substudies addressing the listed research questions. We anticipate a range of publications and conference presentations will result from the study findings. Additionally, recommendations will be made regarding the collection and classification of congenital anomaly data by CP registers.

**DISCUSSION**

This epidemiological study will allow investigation of the co-occurrence of congenital anomalies and CP in the largest population-based sample to date. New knowledge will be generated about the specific anomalies found in CP and outcomes for these children, the risk of CP for those with specific anomalies, and the specific anomalies likely to be on causal pathways to CP. Furthermore, it will develop processes that can be used broadly in CP aetiology research regarding the classification of both single and multiple congenital anomalies.

Variation between registers in inclusion/exclusion criteria, variables collected and their definitions can present a challenge for large collaborative studies. The strengths of our study are the use of strict definitions from established networks (eg, EUROCAT, SCPE and ACPR) and flexibility in which registers are included in individual analyses, which will help to maintain integrity. Another strength is the use of multiple population-based registers which help to minimise bias. Furthermore, by obtaining congenital anomaly data from both CP and congenital anomaly registers, we have the option of including the most comprehensive and highest quality description of prevalence of congenital anomalies. Finally, this will be the first study to report risk of CP for individuals with the congenital anomalies most strongly associated with CP. We seek to build on previous research which reported an increased prevalence of CP for children with congenital anomalies in nervous, cardiovascular, respiratory and musculoskeletal systems.26 By identifying those specific anomalies with the greatest risk of CP, we seek to encourage clinicians and congenital anomaly researchers to be more aware of the potential for CP for these children which may contribute to earlier detection and intervention for CP and better family counselling.

A limitation of our study relates to the different ages when children are included on congenital anomaly and CP registers. CP registers require that a description and clinical presentation of CP is confirmed at age 4 or 5 years, whereas congenital anomalies registers tend to register at an earlier age. Children included in a congenital anomalies register may have migrated out of the region before registration on the equivalent CP register at age 4 or 5, leading to possible underestimation of cases with both CP and congenital anomalies. Migration has a greater impact for registries covering a small geographical region than those covering larger areas. The study is also limited by the inclusion only of regions in Europe and Australia. The epidemiology of both CP and congenital anomalies differs regionally,27 28 particularly between low/middle-income and high-income countries. We will not be able to generalise these findings, especially to low-income and middle-income countries.

We expect there to be substantial differences in the live birth prevalence of congenital anomalies between regions, due to differences in ascertainment, statistical uncertainty due to small numbers, prenatal screening and diagnostics and rates of terminations of pregnancy. Higher rates of terminations with severe, but not necessarily lethal, anomalies could also be one of the factors explaining recently reported reductions in rates of CP in some populations.23

With this large, collaborative study, we hope to gain a comprehensive understanding about the group of children with both CP and major congenital anomalies. Congenital anomalies are routinely listed as exclusion criteria for trials of neuroprotective treatments, yet the primary prevention of congenital anomalies is a focus of several groups worldwide.29 Improved understanding of the causes of co-occurring anomalies and CP is an important step towards identifying new primary prevention strategies specifically for this group.

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4Telethon Kids Institute, University of Western Australia, Perth, Australia
5Paediatric Department, Hospital Lillebaelt Kolding, Kolding, Denmark
6South Australian Birth Defects Register, Women’s and Children’s Hospital, Women’s and Children’s Health Network, Adelaide, South Australia, Australia
7The Cerebral Palsy Register of Norway, Vestfold Hospital Trust, Tønsberg, Norway

**Acknowledgements** We gratefully acknowledge the consumers that have contributed to the study, Professor Christine Cans, who conceived the idea for this collaborative, international study, and Professor Judith Rankin for her thoughtful contributions to a draft of this manuscript. We also acknowledge SCPE, EUROCAT and the ACPR for their support of this project.

**Contributors** SM, GA, EG, EB, SG, GGJ, NB, CG, HS and HS-S contributed to the design of the study. SG is a PhD scholar on the study, supervised by SM and NB. SG, SM and NB are investigators on the NHMRC grants and Cerebral Palsy Alliance Research Foundation PG1215 grants, and SG, SM, GA, EG, GGJ, EB, CB, GS and HS-S are investigators on the Cerebral Palsy Alliance Research Foundation PG2816 grant. SG developed and conducted the original survey to identify potential participating regions, with important input from SM, GGJ, NB, EB, EG, CB, GS, HS-S and GA. SG wrote the first draft of the ethics application, study protocol and this manuscript, with supervision from SM and critical review and contributions from GGJ, NB, EB, EG, GS, CB, HS, HS-S and GA. All authors (SG, GGJ, NB, EG, CB, GS, SM, HS, HS-S and GA) read and approved the final manuscript.

**Funding** This work is supported by the National Health and Medical Research Council of Australia (NHMRC) (Early Career Fellowship 1111270-SM) (Postgraduate research scholarship 1113906-SG) and the Cerebral Palsy Alliance Research Foundation (Project grants PG1215 and PG2816). SM, NB, SG and HS-S receive salary support from the Cerebral Palsy Alliance.

**Disclaimer** The NHMRC and Cerebral Palsy Alliance have no role in the design of the study or data collection, analysis, interpretation of data or manuscript writing.

**Competing interests** None declared.

**Patient consent** Not required.
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