PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A comprehensive investigation of congenital anomalies in cerebral palsy: protocol for a European-Australian population-based data linkage study (The Comprehensive CA-CP Study)
AUTHORS	Goldsmith, Shona; Garcia Jalon, Guiomar; Badawi, Nadia; Blair, Eve; Garne, Ester; Gibson, Catherine; Mcintyre, Sarah; Scott, Heather; Smithers Sheedy, Hayley; Andersen, Guro

VERSION 1 – REVIEW

REVIEWER	Susana Collado-Vázquez Universidad Rey Juan Carlos, Madrid, Spain
REVIEW RETURNED	07-Mar-2018

GENERAL COMMENTS	The authors have not considered as limitation the fact that significant geographic areas are not represented. The discussion is not linked to real results of the study.

REVIEWER	Mary Jane Platt Norwich Medical School, University of East Anglia, Norwich, Norfolk, UK
REVIEW RETURNED	09-Apr-2018

GENERAL COMMENTS	This is a well designed and clearly explained study protocol. The boxes ticked 'No' above are because they are not fully 'Yes' not because they are a significant concern. So for example, one of the research questions states "what is the best..." where 'best' is not fully explained, and rather generic: best in what way? Similarly "what are the clinical outcomes...". again, rather generic. It is also not clear whether the risk estimate proposed in research question (d) relates to possible causal or associative relationships. The authors mention the contributing registers using the same 'methodology' when i think they mean 'methods' (if not, this needs a fuller explanation). The methods mention that all participants will have resided in the region at the time of birth; I am not sure this information is available for all the CP registers (e.g. Rheop). The authors are aware of the potential bias arising from the confirmation of CP at a later age but do not indicate whether they intend to undertake any sensitivity analysis.

VERSION 1 – AUTHOR RESPONSE

Reviewer **Reviewer's comment** **Authors' response to comment**

Reviewer 1	The authors have not considered as limitation the fact that significant geographic areas are not represented	Thank you. In 2016, we published an article titled *An international survey of cerebral palsy registers and surveillance systems.* From this work, we were able to identify potential regions with cerebral palsy (CP) registers to participate in this study. As the majority of the existing CP registers are located in Europe and Australia, we chose these two areas for our current study. Our scoping survey identified European and Australian areas with both a CP and congenital anomaly register. We are not aware of any other regions with co-existing CP and congenital anomaly registers. However, it is certainly true that the inclusion only of Australia and Europe is a limitation of this study. We have included reference to this limitation in the paper (discussion, page 12): *The study is also limited by the inclusion only of regions in Europe and Australia. The epidemiology of both cerebral palsy and congenital anomalies differ regionally,[Khandaker et al, 2015; Christianson et al, 2006] particularly between low or middle and high income countries. We will not be able to generalise these findings, especially to low and middle income countries.* Goldsmith et al, 2016. An international survey of cerebral palsy registers and surveillance systems. Developmental Medicine and Child Neurology; 58(Suppl 2):11-17. Khandaker G et al, 2015. Bangladesh Cerebral Palsy Register (BCPR): a pilot study to develop a national cerebral palsy (CP) register with surveillance of children for CP. BMC Neurology;15:173. Christianson A et al, 2006. Global report on birth defects. White Plains, New York: March of Dimes Birth Defects Foundation.
	The discussion is not linked to real results of the study.	As this protocol manuscript does not have results to draw upon or describe in the discussion, we have focussed on a discussion of the study methods including strengths and limitations.
Reviewer: 2	This is a well designed and clearly explained study protocol. The boxes ticked 'No' above are because they are not fully 'Yes'	Thank you for this feedback.

not because they are a significant concern.

So for example, one of the research questions states "what is the best..." where 'best' is not fully explained, and rather generic: best in what way?

Thank you for this comment. We agree that the first research question*, a) What is the best method of classifying congenital anomalies, including multiple anomalies, when focusing on CP aetiology?* relates more to a process outcome, rather than being a research question as such. Therefore, we have removed this research question from the manuscript (final paragraph, page 5), and updated the numbering of the research questions throughout the paper.

We have retained our references to this being a process outcome from the study: page 11 (Ethics and Dissemination): *Additionally, recommendations will be made regarding the collection and classification of congenital anomaly data by CP registers,* and page 11 (Discussion): *Furthermore, it will develop processes that can be used broadly in CP aetiology research regarding the classification of both single and multiple congenital anomalies.*

Similarly "what are the clinical outcomes...". again, rather generic.

We have clarified the clinical outcomes in line with the collected data, and in line with the statistical analysis plan reported on page 11. The research question now reads (page 6):

c) 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 to children with CP without anomalies?*

It is also not clear whether the risk estimate proposed in research question (d) relates to possible causal or associative relationships.

The risk estimate in research question (d) has been clarified in line with the statistical analysis plan on page 11 (odds ratios (univariate and multivariate) to calculate the odds of CP associated with specific congenital anomalies). The research question (page 6) now reads:

For infants with specific congenital anomalies,

	what is the associated risk of CP?
The authors mention the contributing registers using the same 'methodology' when I think they mean 'methods' (if not, this needs a fuller explanation).	Thank you for identifying this error, we do indeed mean that the contributing registers use the same methods. We have updated the text to read "methods" in the footnotes of Table 1 (page 5) and under Design and setting (paragraph 2), page 6.
The methods mention that all participants will have resided in the region at the time of birth; I am not sure this information is available for all the CP registers (e.g. Rheop).	Thank you for identifying this item requiring additional information. We have clarified this item by adding to the "Participants" (page 6 and 7) section of the manuscript: "born 1991-2009 **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 authors are aware of the potential bias arising from the confirmation of CP at a later age but do not indicate whether they intend to undertake any sensitivity analysis.	In our discussion (page 12), we have indeed referred to the potential bias arising from CP registers verifying data at a later age than congenital anomaly registers. There is the potential underestimation of cases with CP and a congenital anomaly where families have migrated out of a participating region before CP is verified. This is most likely to have an effect on research question (c) – the associated risk of CP for infants with specific congenital anomalies. The impact of migration is a common limitation for register based studies (e.g. Rankin et al, 2008; SCPE Cans et al, 2000). Migration, and its subsequent impact on register data, is likely to differ for each region. A study from southern Sweden, found high net migration INTO the region, possibly due to the availability of health care in the region (Westbom et al, 2009); in-migration would not affect our findings. We are not aware of equivalent Australian data, however one recent paper found families with a child with CP did not appear to move from to less remote areas (de Lacy et al, 2016). It will not be possible with this large, collaborative study to obtain migration data or estimates of missing CP cases related to migration from each region. Therefore, with the limited datasets available we will not be able to undertake sensitivity analysis regarding any effects of migration. The limitation will be discussed in

future results papers.

Rankin J et al, 2008. Congenital anomaly and childhood cancer: a population-based, record linkage study. Pediatric Blood Cancer; 51:608-612.

Surveillance of Cerebral Palsy Europe, Cans, 2000. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Developmental Medicine and Child Neurology; 42: 816-824.

Westbom L et al, 2007. Cerebral palsy in a total population of 4-11 year olds in southern Sweden. BMC Pediatrics; 7:41.

De Lacy et al, 2016. Change in residential remoteness during the first 5 years of life in an Australian cerebral palsy cohort. Developmental Medicine and Child Neurology; 58(Suppl 2):60-65.

VERSION 2 – REVIEW

REVIEWER	Mary Jane Platt Norwich Medical School, University of East Anglia, UK
REVIEW RETURNED	27-May-2018

GENERAL COMMENTS	The authors have clearly and comprehensively adddresed the issues raised in my previous review, and i would now recommend that this paper is accepted