PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for hospital based-surveillance of cerebral palsy (CP) in Hanoi using the Paediatric Active Enhanced Disease Surveillance mechanism (PAEDS-Vietnam): a study towards developing hospital based disease surveillance in Vietnam
AUTHORS	Khandaker, Gulam; Van Bang, Nguyen; Dũng, Trịnh; Giang, Nguyen; Chau, Cao; Van Anh, Nguyen; Van Thuong, Nguyen; Badawi, Nadia; Elliott, Elizabeth

VERSION 1 – REVIEW

REVIEWER	David Bearden University of Rochester School of Medicine USA I am the principal investigator for the Botswana cerebral palsy registry, an ongoing study of cerebral palsy in Botswana.
REVIEW RETURNED	03-Jul-2017

GENERAL COMMENTS	This appears to be a well-designed, and well-thought out study on an important topic. However, the purpose of publishing a protocol in advance of a study being performed is to ensure adequate information is available to interpret the actual study performed. This protocol is missing key information to adequately ascertain that information. The following information should be included with the published protocol: 1) Data collection instruments (preferably) or a detailed description of data and data sources that will be collected should be published. 2) There are no statistical methods included in this protocol, and these should be included. 3) The protocol as described will not allow you to calculate a prevalence, only a "burden of disease" in two tertiary care centers. I am presuming that the authors will utilize some of the epidemiologic methods utilized in the Australian cerebral palsy registry to calculate a prevalence based on a census for the area, but since there are multiple hospitals in the Hanoi area that children with CP could attend, and many children may not have been born in the area but travel to the area for care, I'm not sure how you account for that. More detailed methods for calculating prevalence and accounting for referral bias need to be described fully. 4) The study as described since it is hospital based is likely to oversample children with severe cerebral palsy or with comorbidities such as epilepsy as these children will more often require hospitalization. Additional statistical methods to account for this should be described in the protocol.

	5) Additional details regarding the consent process should be included (e.g. will written informed consent be required? what language will consent be sought in? will you exclude participants who are not fluent in that language?). If culturally appropriate assent should be sought from children who are developmentally able to assent, especially since the study will enroll up to age 18 and many of those children are functionally young adults who presumably would want to have some input into their study participation. 6) Inclusion/exclusion criteria are not sufficiently clear and specific in this protocol. It is stated that local doctors doing the enrollment will be trained on "internationally recognized diagnostic guidelines," these guidelines should be specified as I am not aware of any guidelines that are available for use in low-resource settings. For example, in many low-resource settings children with a variety of conditions such as intellectual disability, neuromuscular disorders, genetic disorders (e.g. trisomy 21, tuberous sclerosis), epilepsy, and traumatic brain injuries are incorrectly diagnosed with cerebral palsy. The protocol should include additional information on how your definition of cerebral palsy is operationalized to ensure that children truly have cerebral palsy, or should make clear that you are embracing a more expansive definition of cerebral palsy. For example, including as inclusion criteria that children should have either weakness or stiffness in at least one limb would ensure that those children with isolated ID or epilepsy would not be incorrectly included. There should be an age limit for onset of symptoms to ensure that children with, say, a TBI at age 5 are not included as having cerebral palsy. Exclusion criteria should be spelled out, e.g. children with known genetic disorders, children with evidence of progressive disorders, children with history of brain malignancies, etc. 7) It is unclear from this protocol who makes the final diagnosis of cerebral palsy. E.g. does the local study physician make the diagnosis? Is that made in consensus with the investigators? 8) It does not appear that there are any pediatric neurologists on the study team. If available, review of cases by a pediatric neurologist would help ensure that the cases are truly cases of cp and not one of the many alternative diagnoses that are possible. 9) It is not spelled out if there is a defined follow up schedule, or how "capture-recapture" would be implemented. Would most children only be seen once, in the hospital setting? It appears that children under the age of 5 would be seen again to confirm the diagnosis once they are over age 5, but are most children going to be seen more than once? 10) The authors might find useful some of the work that has been done in Sub-Saharan Africa regarding studying cerebral palsy in low resource settings. The International Child Neurology Association held a meeting on this topic including a summary of desired data elements, results of which have been published: Donald KA, Samia P, Kakooza-Mwesige A, and Bearden D. Pediatric Cerebral Palsy in Africa: a Systematic Review. Seminars in Pediatric Neurology, 2014 Mar;21(1):30-5. Donald KA, Kakooza AM, Robinson DW, Mallewa M, Samia P, Babakir H, Bearden D, Majnemer M, Fehlings D, Shevell M, Chugani H and Wilmshurst JM. Pediatric Cerebral Palsy in Africa: Where are we? J Child Neurology 2014 Oct 7. pii: 0883073814549245. 11) How will cerebral palsy etiology be determined?

	Do you have prespecified criteria? If so, those should be published with the protocol. If it will be determined by study physician or investigator consensus, that should also be specified.

REVIEWER	RENEVA PETERSEN UNIVERSITY OF CAPE TOWN, SOUTH AFRICA NIL
REVIEW RETURNED	04-Jul-2017

GENERAL COMMENTS	This is important research, thank you for an excellent submission. Please could you look at some elements of phrasing/grammar in your introduction which could benefit from editing. line 20-27 line 52-57

REVIEWER	Mary Jane Platt Norwich Medical School, University of East Anglia, Norwich, UK
REVIEW RETURNED	17-Jul-2017

GENERAL COMMENTS	1. The protocol clearly outlines the aims of the study as a. implement hospital-based surveillance system for CP b. collect data on those presenting with CP c. assess whether this process can be rolled out for the whole of Vietnam Furthermore it identifies some specific objectives including a. estimating the burden of CP b. defining its aetiology c.describing motor impairment, severity, and associated impairments, the nutritional and rehabilitation status of affected children d. evaluate whether this process works as a hospital-based disease surveillance system 2.However, although alluded to, these are not specified in the abstract I have a few concerns about protocol: • There is no statement of the anticipated duration of this proposal. Although I assume that the authors are hoping that this will be a continued process it is important to identify the planned duration of this initial, pilot phase. Furthermore, there is no estimate of the likely number of children with CP likely to be included in this surveillance study, and therefore no sample size or power calculations to enable whether the likely precision with which the parameters can be estimated are likely to be meaningful. • Although this surveillance study will collect information on those with CP attending the hospitals, it is unclear from the proposal whether the authors recognise the limitations of a hospital-based surveillance system compared with a population based surveillance system: it is only the latter that will provide information on the prevalence of CP in the population (and other variables related to this), alluded to in the introduction, e.g. proportion of affected children receiving rehabilitation.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment 1: Data collection instruments (preferably) or a detailed description of data and data sources that will be collected should be published.
Our response: We have added the study questionnaire/data collection instrument as supplementary study material (Appendix A).

Comment 2: There are no statistical methods included in this protocol, and these should be included.

Our response: We have added a subsection in methods on "statistical methods". (page 9)

Comment 3: The protocol as described will not allow you to calculate a prevalence, only a "burden of disease" in two tertiary care centers. I am presuming that the authors will utilize some of the epidemiologic methods utilized in the Australian cerebral palsy registry to calculate a prevalence based on a census for the area, but since there are multiple hospitals in the Hanoi area that children with CP could attend, and many children may not have been born in the area but travel to the area for care, I'm not sure how you account for that. More detailed methods for calculating prevalence and accounting for referral bias need to be described fully.

Our response: Thank you for this helpful comment. We have provided detailed information in the "statistical methods" section on how prevalence will be estimated for Hanoi province. This is based on the methods previously used by our group for estimating prevalence of congenital rubella syndrome in Hanoi (new reference 20) . We will document the children's address (district, province) to enable identification and of children coming from outside the Hanoi region and their exclusion from estimates of prevalence. (page 9)

Comment 4: The study as described since it is hospital based is likely to oversample children with severe cerebral palsy or with comorbidities such as epilepsy as these children will more often require hospitalization. Additional statistical methods to account for this should be described in the protocol.

Our response: We agree that this is an inherent limitation of hospital based surveillance compared with population based surveillance. We have identified the potential for selection bias in a subsection on "study limitation". (page 11)

Comment 5: Additional details regarding the consent process should be included (e.g. will written informed consent be required? what language will consent be sought in? will you exclude participants who are not fluent in that language?). If culturally appropriate assent should be sought from children who are developmentally able to assent, especially since the study will enroll up to age 18 and many of those children are functionally young adults who presumably would want to have some input into their study participation

Our response: We have added the following details of the consent process;
Written consent for study participation will be obtained by Vietnamese Surveillance Medical Officers (i.e. third party) using participation information and consent forms written in Vietnamese. The treating physician will then complete the data collection form. The Surveillance Medical Officers will not have any role in patients clinical care, thus coercion is unlikely and participation will not influence clinical care.
Children with cerebral palsy aged less than 18 years will be recruited in this study and parental consent alone will be sought for two reasons;

a. Children with cerebral palsy often have intellectual/cognitive impairment and their ability to give informed consent is variable and uncertain.
b. Children aged less than 18 years are considered minors in Vietnam, requiring their parents/primary care givers to take full responsibility/authority for any decisions related to their medical care and participation in research.
However, children aged over 14 years and with an appropriate comprehension level will be assed for assent. To consider a child for assent the study investigators will take into account the child's age, maturity, and psychological state to determine whether the child is capable of giving a meaningful assent. (page 8)

Comment 6: Inclusion/exclusion criteria are not sufficiently clear and specific in this protocol. It is stated that local doctors doing the enrolment will be trained on "internationally recognized diagnostic guidelines," these guidelines should be specified as I am not aware of any guidelines that are available for use in low-resource settings. For example, in many low-resource settings children with a variety of conditions such as intellectual disability, neuromuscular disorders, genetic disorders (e.g. trisomy 21, tuberous sclerosis), epilepsy, and traumatic brain injuries are incorrectly diagnosed with cerebral palsy. The protocol should include additional information on how your definition of cerebral palsy is operationalized to ensure that children truly have cerebral palsy, or should make clear that you are embracing a more expansive definition of cerebral palsy. For example, including as inclusion criteria that children should have either weakness or stiffness in at least one limb would ensure that those children with isolated ID or epilepsy would not be incorrectly included. There should be an age limit for onset of symptoms to ensure that children with, say, a TBI at age 5 are not included as having cerebral palsy. Exclusion criteria should be spelled out, e.g. children with known genetic disorders, children with evidence of progressive disorders, children with history of brain malignancies, etc.

Our response: Thank you for this helpful comment. We agree that there is a potential for misclassification. However, as the participants will be recruited to tertiary paediatric care centres in Hanoi with advanced neurology and radiology services, we are confident that we clinicians will be able to accurately diagnose children with CP by following the Surveillance of Cerebral Palsy in Europe (SCPE) guideline. Clinical data on all cases identified will be reviewed by the investigator group for potential misdiagnosis. As suggested, we have added more specific details on exclusion criteria to make it clear. (page 7)

Comment 7: It is unclear from this protocol who makes the final diagnosis of cerebral palsy. E.g. does the local study physician make the diagnosis? Is that made in consensus with the investigators?

Our response: Local study physicians (e.g. general paediatricians, rehabilitation paediatricians, paediatric neurologists) will make the diagnosis of CP or confirm the diagnosis on referred cases. They will be trained in use of the SCPE protocol and the recently published CP diagnostic algorithm (new reference 19: Novak I, Morgan C, Adde L. et al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy: Advances in Diagnosis and Treatment. JAMA Pediatr. 2017 Jul 17.). As stated in the response above, clinical data on all cases identified will be reviewed by the investigator group for potential misdiagnosis. In contentious cases the opinion of a paediatric neurologist will be sought. (page 8-9)

Comment 8: It does not appear that there are any pediatric neurologists on the study team. If available, review of cases by a pediatric neurologist would help ensure that the cases are truly cases of cp and not one of the many alternative diagnoses that are possible.

Our response: The local study team will work closely with paediatric neurologists who will also be trained in use of the study protocol and CP diagnostic criteria's. However, we fully agree with the reviewer that involving a paediatric neurologist as an investigator would improve the quality of case ascertainment. We will do this during study implementation. Thank you!

Comment 9: It is not spelled out if there is a defined follow up schedule, or how "capture-recapture" would be implemented. Would most children only be seen once, in the hospital setting? It appears that children under the age of 5 would be seen again to confirm the diagnosis once they are over age 5, but are most children going to be seen more than once?

Our response: Most children will be followed clinically in the hospital setting until therapy is established. Only those children aged less than 5 years will be specifically followed up by the investigator team to confirm the diagnosis once they are over age 5. The case register will be amended as required. (Page 7)

Comment 10: The authors might find useful some of the work that has been done in Sub-Saharan Africa regarding studying cerebral palsy in low resource settings. The International Child Neurology Association held a meeting on this topic including a summary of desired data elements, results of which have been published:
Donald KA, Samia P, Kakooza-Mwesige A, and Bearden D. Pediatric Cerebral Palsy in Africa: a Systematic Review. Seminars in Pediatric Neurology, 2014 Mar;21(1):30-5.
Donald KA, Kakooza AM, Robinson DW, Mallewa M, Samia P, Babakir H, Bearden D, Majnemer M, Fehlings D, Shevell M, Chugani H and Wilmshurst JM. Pediatric Cerebral Palsy in Africa: Where are we? J Child Neurology 2014 Oct 7. pii: 0883073814549245.

Our response: Thank you for referring us to these very helpful publications. We have referred to one of these papers in our background (new reference 3: Donald KA, Samia P, Kakooza-Mwesige A, and Bearden D. Pediatric Cerebral Palsy in Africa: a Systematic Review. Seminars in Pediatric Neurology, 2014 Mar;21(1):30-5.).

Comment 11: How will cerebral palsy etiology be determined? Do you have pre specified criteria? If so, those should be published with the protocol. If it will be determined by study physician or investigator consensus, that should also be specified.
Our response: Aetiology of CP will be determined based on clinical history and review of medical records and investigations. The attached questionnaire (Appendix A) contains the pre-specified criteria for aetiology. It will be completed by the study physicians who will be trained in using the study protocol. For complex cases, aetiology will be determined by investigator group consensus. Our experience in Bangladesh shows that in many cases a definite aetiology could not be established.

Reviewer 2

Comment 1: This is important research, thank you for an excellent submission. Please could you look at some elements of phrasing/grammar in your introduction which could benefit from editing.
line 20-27, line 52-57

Our response: Thank you for this helpful comment. We have paraphrased the suggested sections.

Reviewer: 3

Comment 1: There is no statement of the anticipated duration of this proposal. Although I assume that the authors are hoping that this will be a continued process it is important to identify the planned duration of this initial, pilot phase.
Furthermore, there is no estimate of the likely number of children with CP likely to be included in this surveillance study, and therefore no sample size or power calculations to enable whether the likely precision with which the parameters can be estimated are likely to be meaningful.

Our response: Thank you for this helpful comment. We have added a subsection "study duration" and added the following statement for clarification;
The pilot phase of the study will be for six months. During this period we will train the study investigators, participating physicians and develop the study implementation tools. Moreover, during the pilot phase we will have a better understanding on the case load (i.e. number of children with CP seeking medical care at the participating hospitals). After the pilot phase we will conduct an interim evaluation of the surveillance mechanism. Once the pilot phase is successfully implemented surveillance will be continued for another 18 months. The PAEDS-Vietnam mechanism will remain in place for potential use in other conditions. (page 10)

Comment 2: Although this surveillance study will collect information on those with CP attending the hospitals, it is unclear from the proposal whether the authors recognise the limitations of a hospital-based surveillance system compared with a population based surveillance system: it is only the latter that will provide information on the prevalence of CP in the population (and other variables related to this), alluded to in the introduction, e.g. proportion of affected children receiving rehabilitation.

Our response: We have added a subsection on "Study limitations" and added the following statement; Hospital based surveillance of children with CP will likely overestimate children with severe CP or with co-morbidities such as epilepsy as these children more often require hospitalization. Moreover, we would not be able precisely estimate the prevalence of CP as it is unlikely that all the children with CP will seek medical care in the participating hospitals. (page 11)

VERSION 2 – REVIEW

REVIEWER	David Bearden University of Rochester School of Medicine, USA I am the Principal Investigator of the Botswana cerebral palsy registry.
REVIEW RETURNED	22-Aug-2017

GENERAL COMMENTS	I appreciate that the authors have addressed all my concerns and suggestions. I have no further comments.