PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Improving epilepsy control among children with cerebral palsy in rural Bangladesh: A prospective cohort-based study
AUTHORS	Karim, Tasneem; Das, Manik Chandra; Muhit, Mohammad; Badawi, Nadia; Khandaker, Gulam; Mohammad, Shekeeb S

VERSION 1 – REVIEW

REVIEWER	Kwan, Patrick Alfred Hospital, Department of Neurology
REVIEW RETURNED	22-Jun-2021

GENERAL COMMENTS	This is a descriptive audit of an epilepsy management program for children with cerebral palsy in a rural community in Bangladesh. Those who had a diagnosis of epilepsy were reviewed by health workers trained by a pediatric neurologist from Australia, who supervised in person the review of each child in a dedicated epilepsy clinic. After the clinic assessments the diagnosis for some of the children was revised and the treatments were changed. The children were then followed up by telephone visit by community health workers, as well as a single telemedicine visit joined by the pediatric neurologist in Australia. Overall the report is well written and gives a flavor of the various medical and non-medical constraints in managing this group of very challenging children. My comments and questions are mainly around clarification of methodology. Introduction “Studies show that epilepsy is associated with greater impairment of cognitive function, poorer motor outcomes, more profound behavioral and psychological problems, and poorer quality of life among children with CP, all of which collectively contribute to a greater burden of disability and care [2].” Is this in comparison with epilepsy in children without CP, or children with CP but without epilepsy? “Children with CP and epilepsy tend to have early onset of seizures which can often be difficult to control [3].” Likewise, is this compared with children without CP? Methods What are BCPR “camps”? How was the original diagnosis of epilepsy made? Diagnosis of epilepsy was based on “history of one or more unprovoked seizures in the previous 3 months recorded by medical practitioners”. This does not conform with the current ILAE

	criteria for diagnosing epilepsy. There is a likelihood of misdiagnosis, both underdiagnosis (e.g. children who had recurrent seizures before 3 months), and overdiagnosis if the medical practitioners were not trained in the diagnosis of epilepsy. "Specialist clinical assessments at the clinics were overseen by a pediatric neurologist from Australia". I assume this neurologist is one of the authors? Can you provide the initials of the neurologist? Figure 1. Unless I have misunderstood only 15 minutes was spent for clinical review for each patient. Part of the time would be taken up by interpretation. This is far less that typically required based on this reviewer's personal experience. Considering the level of details in the proforma I am concerned that this would not be sufficient to adequately review the typically complex medical history of this patient population, casting further concern over the epilepsy diagnosis and seizure classification. What was the purpose of the phone follow-up and the telemedicine clinics? Were they purely for data collection or for clinical management? It appears that latter started after end of the patient recruitment period? Results Was age normally distributed? If not, it would be more appropriate to provide median and range. Seizure classification terminology should conform to the latest ILAE scheme (2017). How many had multiple seizure types? "Seizures were already controlled with AED in 5.8%". How was "controlled" defined? Seizure classification was purely based on history taking. Was a witness always available during the consultation? Without support from EEG it is challenging to make a definitive classification based on history alone. Of the 7 patients assessed to have been misdiagnosed to have epilepsy and treated with AEDs, were there any changes to their AED treatment? Was treatment withdrawn and what were these patients' outcomes? What was the range of the phone follow up period? How was seizure control measured, and over what period of time? How was seizure reduction measured? How was 'seizure free' defined? For many children with CP and epilepsy, seizures may not be the only or main problem affecting their quality of life. Were other types of outcomes assessed, e.g. global development, functional level, cognition, or caregiver's impression more broadly? Telemedicine clinics. Only process but no results are presented. It is difficult to see how this part fits in with the rest of the study. Unless results are presented this part should be omitted (in both the methods and results sections).

	Discussion Can the authors discuss the sustainability of the model with experts in Australia providing ongoing support?

REVIEWER	Martin, Katherine Nottingham University Hospitals NHS Trust, Paediatric Neurosciences
REVIEW RETURNED	29-Jul-2021

GENERAL COMMENTS	This is an interesting study and highlights the wider issues faced in countries where family finances as well as clinical need have impact on treatment strategies. Could you comment on the diagnosis of epilepsy apparently being made after just one unprovoked seizure for children on the register, whether this is due to a different definition being used and whether this might have any impact on findings if study is replicated elsewhere? I am interested in the apparently low rate of epilepsy in children with CP in this cohort as you highlight too. Are there any factors that might influence the rate of either true prevalence or apparent prevalence of epilepsy in the group you study? Is there for example an over representation of children with the subtypes of CP that are less likely to have epilepsy as a comorbidity? On p7 line 5 you comment on 'seizure control' being a term to mean no seizures since the last appointment but in the results also use a relative reduction in seizures as a method of assessing control - it might be helpful to clarify / use consistent terminology.

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1
Prof. Patrick Kwan, Alfred Hospital, Monash University Central Clinical School

Comment 1. Introduction “Studies show that epilepsy is associated with greater impairment of cognitive function, poorer motor outcomes, more profound behavioral and psychological problems, and poorer quality of life among children with CP, all of which collectively contribute to a greater burden of disability and care [2].” Is this in comparison with epilepsy in children without CP, or children with CP but without epilepsy?
Response: Thank you for your comment. We have revised the statement as follows to clarify the comparison to children with CP but without epilepsy.

‘Studies show that epilepsy among children with CP is associated with greater impairment of cognitive function, poorer motor outcomes, more profound behavioral and psychological problems, and poorer quality of life, all of which collectively contribute to a greater burden of disability and care [2].’

Comment 2. “Children with CP and epilepsy tend to have early onset of seizures which can often be difficult to control [3].” Likewise, is this compared with children without CP?
Response: This is a comparison to children with epilepsy without CP. We edited the statement as follows for greater clarity,

“In comparison to children with epilepsy only, children with CP and epilepsy tend to have early onset of seizures which can often be difficult to control [3].”

Comment 3. Methods: What are BCPR “camps”? How was the original diagnosis of epilepsy made?
Response: BCPR camps refer to the medical assessment camps conducted on a regular basis in the surveillance sites for BCPR. A multidisciplinary medical assessment team including a paediatrician, a physiotherapist, and a counsellor conducted detailed assessment for data collection for the BCPR. Data on the presence of associated impairments including epilepsy were documented based on review of limited available medical records, report by the parents or primary caregivers of the children with CP, and clinical assessment by the medical assessment team. Detailed account of the BCPR study protocol and findings have been described in previous publications. We elaborated on this for greater clarity in the manuscript.

Comment 4. Diagnosis of epilepsy was based on “history of one or more unprovoked seizures in the previous 3 months recorded by medical practitioners”. This does not conform with the current ILAE criteria for diagnosing epilepsy. There is a likelihood of misdiagnosis, both underdiagnosis (e.g. children who had recurrent seizures before 3 months), and overdiagnosis if the medical practitioners were not trained in the diagnosis of epilepsy.
Response: We acknowledge the chances of underdiagnosis and overdiagnosis. During the epilepsy clinics supervised by a paediatric neurologist (SM) our findings suggested that there was overdiagnosis in some cases in preceding camps as the reviewer has rightly suggested. We have retained the description to reflect what was the practice in our camps preceding the epilepsy focused camps but have acknowledged this as a limitation in the study limitations section.

Comment 5. “Specialist clinical assessments at the clinics were overseen by a pediatric neurologist from Australia”. I assume this neurologist is one of the authors? Can you provide the initials of the neurologist?
Response: Thanks, we have added the paediatric neurologist’s initials, SM, in the text.

Comment 6. Figure 1. Unless I have misunderstood only 15 minutes was spent for clinical review for each patient. Part of the time would be taken up by interpretation. This is far less that typically required based on this reviewer’s personal experience. Considering the level of details in the proforma I am concerned that this would not be sufficient to adequately review the typically complex medical history of this patient population, casting further concern over the epilepsy diagnosis and seizure classification.
Response: Thanks for helping us clarify this point. Our assessments were based on a staggered approach where we used datapoints from previous information on each patient and also utilised a multistep model in the clinical reviews which we have tried to explain better. The background for each patient was known from previously compiled BCPR data and this was reviewed by the clinicians prior to the clinics. The clinicians additionally had access to the BCPR data of each child during the clinical review.

At the clinics, a trained community therapist partially completed the proforma including measurement of weight and documentation of drug history of each child at first in the clinic waiting room. This was followed by the 15 minutes for clinical review by the physicians which was used for detailed history taking, review of existing relevant medical records, and the prescription was written out within this time. This was then followed by 5 to 10 minutes with the community therapist during which he explained the prescribed medications to the primary caregiver. This has been outlined in Figure 1.

Comment 7. What was the purpose of the phone follow-up and the telemedicine clinics? Were they purely for data collection or for clinical management? It appears that latter started after end of the patient recruitment period?
Response: We used the phone follow up for collection of data on compliance and for checking for change in seizure frequency and presence/absence of any side effects as outlined in the Phone follow up section but further explained in Appendix C. In reality the purpose of the telemedicine clinics was to start building a system of telemedicine clinic and train local practitioners through mentoring by SM – paediatric neurologist from Australia. The vision remains that a model based on telemedicine can support evaluation and follow up of this cohort with gradual building up of local skills and retained oversight by a specialist. This, however, was disrupted by the COVID-19 pandemic when the local practitioners and families could not continue travelling as regularly for the clinics. We have now removed the telemedicine section from the results and briefly outlined in the discussion.

Comment 8. Results: Was age normally distributed? If not, it would be more appropriate to provide median and range.
Response: Thank you, we ensured that reporting is consistent with the distribution of the data.

Comment 9. Seizure classification terminology should conform to the latest ILAE scheme (2017).
Response: Thank you, we have amended the seizure terminology to reflect the 2017 ILAE scheme.

Comment 10. How many had multiple seizure types?
Response: Thank you, we have added this information 11.6% (12/103) had multiple seizure types.

Comment 11. “Seizures were already controlled with AED in 5.8%”. How was “controlled” defined?
Response: Thank you for the comment. Controlled was defined as no witnessed seizures by primary caregiver/family members for the past one month at the time of clinical review. Controlled refers to complete cessation of seizures rather than reduction.

Comment 12. Seizure classification was purely based on history taking. Was a witness always available during the consultation? Without support from EEG, it is challenging to make a definitive classification based on history alone.
Response: The primary caregiver was always present. Records from the BCPR and any existing medical records were used to corroborate history and clinical characteristics. EEG could not be done as part of this study, however, if any child had previous EEG reports they were reviewed by the team. We predominantly had to rely on history taking in our study setting. The clinic site in Shahjadpur subdistrict of Sirajganj is located in the northern part of Bangladesh. Majority of our study participants were living below the national poverty line and could not access or afford EEG. The primary caregivers often rely on daily work for day to day income and travelling for even clinic reviews to neighbouring cities is not feasible. In this setting, while not ideal and complete, clinical evaluations remain the best compromise in assessing children including for epilepsy.

Comment 13. Of the 7 patients assessed to have been misdiagnosed to have epilepsy and treated with AEDs, were there any changes to their AED treatment? Was treatment withdrawn and what were these patients’ outcomes?

Response: Thank you for the comment. AED was stopped for all seven of them. At follow up none of them worsened, thereby, further confirming the misdiagnosis of epilepsy and unnecessary administration of AED to these children. We have added this information to the results section.

Comment 14. What was the range of the phone follow up period?
Response: Thank you for the comment. The range of phone follow up period was six months from the time of the clinical review. We have added this information to the phone follow up section.

Comment 15. How was seizure control measured, and over what period of time? How was seizure reduction measured? How was 'seizure free' defined?
Response: Control and reduction both measured by clinical history on follow up. Seizure freedom has been defined as no seizure between the clinic and follow up.

Comment 16. For many children with CP and epilepsy, seizures may not be the only or main problem affecting their quality of life. Were other types of outcomes assessed, e.g. global development, functional level, cognition, or caregiver's impression more broadly?
Response 16. Thank you. The BCPR team has multiple ongoing projects. Outcomes including quality of life, functional outcomes and caregivers' wellbeing have been reported by on other studies (see references below). We plan to link to epilepsy outcomes to other outcomes among children with CP in the future.

Power R, Galea C, Muhit M, Heanoy E, Karim T, Badawi N, Khandaker G. What predicts the proxy-reported health-related quality of life of adolescents with cerebral palsy in Bangladesh?. BMC public health. 2020 Dec;20(1):1-0.
Power R, Muhit M, Heanoy E, Karim T, Badawi N, Akhter R, Khandaker G. Health-related quality of life and mental health of adolescents with cerebral palsy in rural Bangladesh. PLoS One. 2019 Jun 11;14(6):e0217675.
Karim T, Muhit M, Jahan I, Galea C, Morgan C, Smithers-Sheedy H, Badawi N, Khandaker G. Outcome of Community-Based Early Intervention and Rehabilitation for Children with Cerebral Palsy in Rural Bangladesh: A Quasi-Experimental Study. Brain sciences. 2021 Sep;11(9):1189.

Comment 17. Telemedicine clinics. Only process but no results are presented. It is difficult to see how this part fits in with the rest of the study. Unless results are presented this part should be omitted (in both the methods and results sections).
Response: Thank you. We have removed the telemedicine clinics from the methods and results as suggested and briefly outline our approach and intention with this in the discussion.

Comment 18. Discussion - Can the authors discuss the sustainability of the model with experts in Australia providing ongoing support?
Response: One of the major aims of this study was to upskill local health practitioners. The study team including the expert in Australia supported local capacity building and the development of a guideline for the management of epilepsy among children with CP in such settings. We believed sustainability would improve further in the near future with the collaborative efforts already in place through multiple ongoing projects to support the children with CP and their families in the study site. The global pandemic has demonstrated the power of telehealth and we had already realised this pre-pandemic in our pilot telehealth clinics. We believe that remote oversight by specialists and allied professional in resource sufficient settings is a way forward to assist clinical upskilling and care

provision in resource poor settings without the barriers of repeated international travel and multi-day commitments.

REVIEWER 2
Dr. Katherine Martin, Nottingham University Hospitals NHS Trust

Comment 1. Could you comment on the diagnosis of epilepsy apparently being made after just one unprovoked seizure for children on the register, whether this is due to a different definition being used and whether this might have any impact on findings if study is replicated elsewhere?
Response: This is the definition for epilepsy that had been used in relation to the Bangladesh CP register as part of the ongoing population-based surveillance. In the clinics conducted as part of this study the ILAE definition has been used.

Comment 2. I am interested in the apparently low rate of epilepsy in children with CP in this cohort as you highlight too. Are there any factors that might influence the rate of either true prevalence or apparent prevalence of epilepsy in the group you study? Is there for example an over representation of children with the subtypes of CP that are less likely to have epilepsy as a comorbidity?
Response: Thank you. The rate of epilepsy observed among children with CP in our study is consistent with rates reported in other low resource settings such as Indonesia where 13.5% of children with CP had epilepsy However, the rates of epilepsy documented among children with CP from different studies often vary. We speculate this is due to methodological differences and the use of variable definitions of epilepsy across studies. Furthermore, there is a growing body of evidence on the differences in the prevailing risk factors, and timing of acquisition of CP among children in low resource settings compared to high income countries. These factors are often associated with varied likelihood of having epilepsy, therefore, contribute further to the wide-ranging reported rates of epilepsy among children with CP globally. We updated sections of the discussion to reflect these.

Comment 3. On p7 line 5 you comment on 'seizure control' being a term to mean no seizures since the last appointment but in the results also use a relative reduction in seizures as a method of assessing control - it might be helpful to clarify / use consistent terminology.
Response: Thank you. We ensured consistent terminology throughout the manuscript. Seizure control is used to describe seizure freedom and reduction is used to describe improvement but not seizure freedom.

VERSION 2 – REVIEW

REVIEWER	Kwan, Patrick Alfred Hospital, Department of Neurology
REVIEW RETURNED	10-Dec-2021

GENERAL COMMENTS	The authors have addressed my comments well.

REVIEWER	Martin, Katherine Nottingham University Hospitals NHS Trust, Paediatric Neurosciences
REVIEW RETURNED	18-Dec-2021

GENERAL COMMENTS	Thank you for addressing so clearly the queries raised in the first reviews. There are a very few minor grammatical issues (mainly missing words) which should be apparent on final proof reading.