

PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	A PROSPECTIVE OBSERVATIONAL STUDY OF ADVERSE DRUG REACTIONS OF ANTIEPILEPTIC DRUGS IN CHILDREN IN THE UNITED KINGDOM
AUTHORS	Choonara, Imti; Egunsola, Oluwaseun; Sammons, Helen; Ojha, Shalini; Whitehouse, William; Anderson, Mark; Hawcutt, Dan

VERSION 1 - REVIEW

REVIEWER	Verrottidianella, Alberto University of L' Aquila, Italy Competing interests: pediatric epilepsy
REVIEW RETURNED	08-Jun-2017

GENERAL COMMENTS	<p>The authors report the data of a multicentre prospective cohort study on three thousand children on AED drug treatment in hospitals across the United Kingdom.</p> <p>Overall the paper is well written with a logical smooth flow. The data are clearly presented.</p> <p>However, in my opinion, there is no detailed discussion and no comparison with previous data from literature has been performed. I suggest to work on this part of the paper. Also some practical advices (based on the results of this study) can be useful for the readers.</p>
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REVIEWER	Jansen, Katrien UZ Leuven, Belgium Competing interests: no
REVIEW RETURNED	09-Jun-2017

GENERAL COMMENTS	<p>The subject is worthwhile to investigate, but the study design and objectives are not new.</p> <p>Many ADRs are seen in the first weeks of treatment and can be temporarily, it is not clear in the FU scheme how this will be monitored and if treatment will be adjusted.</p> <p>It is not clear how secondary objectives will be investigated: for instance preventability of ADRs will be determined?</p> <p>Will they include genetic testing before use of carbamazepine?</p> <p>The PESQ score is very difficult to apply in patients with severe mental retardation, most of the problems will be due to the epileptic encephalopathy.</p>
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REVIEWER	Putignano, Daria Department of Public Health Laboratory for Mother and Child Health
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	IRCCS - Mario Negri Pharmacological Research Institute Competing interests: No conflict of interest
REVIEW RETURNED	19-Jun-2017

GENERAL COMMENTS	<p>The introduction of the protocol is well structured and prepared following an updated review of the literature. The gap of knowledge is clear, but it should be explained more clearly why you want to first publish the study protocol.</p> <p>The enrolment and follow-up periods are in line with what has already been published internationally. In the section on the design of the study it is not clear that this is a protocol and not a prospective multicentre study.</p> <p>The method used to identify incident patients (wash out period) should be added.</p> <p>Before the section on statistical analysis, a section on outcome evaluation methods should be added. This section should include ADR surveillance section and additional explanations about the methods applied to calculate incidence, monotherapy and polytherapy and discontinuation rates.</p> <p>The abstract should also be modified consistently with changes in the text.</p> <p>I approve with minor revision the publication of protocols with the aim of increasing information and knowledge on current studies. They represent the starting point for a collective critical evaluation of paediatric research.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

The authors report the data of a multicentre prospective cohort study on three thousand children on AED drug treatment in hospitals across the United Kingdom.

Overall the paper is well written with a logical smooth flow. The data are clearly presented.

However, in my opinion, there is no detailed discussion and no comparison with previous data from literature has been performed. I suggest to work on this part of the paper. Also some practical advices (based on the results of this study) can be useful for the readers.

WE HAVE ADDED PROTOCOL TO THE TITLE TO AVOID CONFUSION

Reviewer: 2

Comments to the Author

The subject is worthwhile to investigate, but the study design and objectives are not new.

Many ADRs are seen in the first weeks of treatment and can be temporarily, it is not clear in the FU scheme how this will be monitored and if treatment will be adjusted.

WE HAVE ADDED A SENTENCE STATING THAT BY HAVING 3 FOLLOW UP VISITS WE WILL IDENTIFY TRANSIENT ADRs (p8)

It is not clear how secondary objectives will be investigated: for instance preventability of ADRs will be determined?

WE HAVE EXPANDED THE SECTION ON PREVENTABILITY OF ADRs (p12)

Will they include genetic testing before use of carbamazepine?

THIS IS NOT ROUTINE PRACTICE IN THE UK

The PESQ score is very difficult to apply in patients with severe mental retardation, most of the problems will be due to the epileptic encephalopathy.

WE AGREE BUT THIS STUDY WILL EVALUATE THE PESQ IN ALL THE PTS WITH EPILEPSY (p3)

Reviewer: 3

Comments to the Author

The introduction of the protocol is well structured and prepared following an updated review of the literature. The gap of knowledge is clear, but it should be explained more clearly why you want to first publish the study protocol.

WE HAVE EXPANDED THE INTRODUCTION TO EXPLAIN THE BENEFIT OF THE STUDY (p3)

The enrolment and follow-up periods are in line with what has already been published internationally. In the section on the design of the study it is not clear that this is a protocol and not a prospective multicentre study.

WE HAVE ADDED THAT IT IS A PROTOCOL TO THE TITLE, ABSTRACT AND STUDY DESIGN

The method used to identify incident patients (wash out period) should be added.

WE HAVE AMENDED THE SECTION ON ADR SURVEILLANCE AND EXPLAINED HOW INCIDENCE AND DISCONTINUATION WILL BE CALCULATED

Before the section on statistical analysis, a section on outcome evaluation methods should be added. This section should include ADR surveillance section and additional explanations about the methods applied to calculate incidence, monotherapy and polytherapy and discontinuation rates.

WE HAVE MADE THESE CHANGES

The abstract should also be modified consistently with changes in the text.

WE HAVE AMENDED THE ABSTRACT

I approve with minor revision the publication of protocols with the aim of increasing information and knowledge on current studies. They represent the starting point for a collective critical evaluation of paediatric research.

Editor's Comments to Author:

Associate Editor

Comments to the Author:

this study protocol has been reviewed by 3 external reviewers and all provide useful comments to further improve the paper although my not fully sure if the first reviewer understood that this was a study protocol, and not a result paper. The comments related to several method related aspects are very useful to further improve the paper

WE HAVE TRIED TO ADDRESS ALL THE POINTS