PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence of adverse events in antipsychotic-naïve children and adolescents treated with antipsychotic drugs: a French multicenter naturalistic study protocol (ETAPE).
AUTHORS	MENARD, Marie-Line; THÜMMLER, Susanne; GIANNITELLI, Marianna; OLLIAC, Bertrand; BONNOT, Olivier; COHEN, David; ASKENAZY, Florence

VERSION 1 - REVIEW

REVIEWER	Soumitra Shankar Datta Senior Consultant Psychiatrist Tata Medical Center, Kolkata India Visiting Researcher - a) IOPPN at the Maudsley, Kings College London b) Institute of women's health, University College London I am a lead reviwer for Cochrane Schizophrenia Group. I have no other competing interest.
REVIEW RETURNED	17-Jan-2016

GENERAL COMMENTS	The current study will add important information to the field child and adolescent psychiatry - especially in the naturalistic setting. However I have a few queries and suggestions: 1. It would be better to change the title to "Incidence of adverse events in drug-naïve children and adolescents treated with antipsychotic drugs: a French multicentre naturalistic study protocol (ETAPE)". 2. The keywords could include: "children" and "adolescents" instead of “paediatric population” as in the world of child psychiatry usual convention in to search with these words as opposed to "paediatrics" only. 3. One of the questions that came to my mind - Why are the authors trying to publish a protocol in December 2015 when as per the www.clinicaltrials.gov the study was contemplated to be completed in Dec 2015. If most of the study period is over, there is very little value in publishing a protocol at this stage and may in some way make the readers feel that this is a prospective declaration by the authors regarding their primary and secondary analysis even before the study began recruitment of subjects. That was the original justification of publishing protocols early. 4. Age group: The www.clinicaltrials.gov mention the age of recruitment of patients of the trial number (NCT02007928) to be 13-17. This was published in Dec 2013 after the study was started around July 2013. The current protocol mentions the age group that will be recruited for the same study to be 6 to 18 years. If there is an amendment this should be updated in the Clinical trials registry.

	5. Validity of certain instruments in the current age group (6-18 years): If the age group included for the current study is indeed 6-18 years, would the original instruments (e.g. Barne's Akathisia scale) be valid in this age group? Few studies on childhood onset schizophrenia (COS) use these instruments. In these trials, although the onset may be in childhood, the age of the children may be more than 10 years when the children are recruited. The current study is on drug naive children and so may potentially recruit children younger (than most trials on COS etc) and will also include other diagnoses other than COS. Will Barne's Akathisia scale be a valid way to assess akathisia in a 7 year old boy with autism and behaviour problems on Risperidone? As a child psychiatrist I do have my doubts. 6. Use of the word 'qualitative': Under measures the authors express that they will be using qualitative measures. In the strict sense of the term, rating scales as Paediatric Adverse Events Rating Scale is a quantitative measure. Please just mention - 'Questionnaires to be used'.

REVIEWER	Marinos Kyriakopoulos South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology and Neuroscience, King's College London
REVIEW RETURNED	30-Jan-2016

GENERAL COMMENTS	This is the protocol of an interesting naturalistic study on the adverse effects of antipsychotic medication in children and young people. The protocol describes the rationale, methodology and outcomes of the study well. It would be of interest to the readership of BMJ Open. I have a few minor suggestions to the protocol authors: - In the title, it would be preferable if they replace "naïve" with "antipsychotic naïve" - In Table 1, line 10: Do the authors mean "height" when they say "size"? Please clarify and replace if this is what they mean. - In Table 1, line 20: Please replace "complete blood count" with "full blood count" - I suspect that the detailed study documents will be in a supplement rather than the main text. Please clarify.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
However I have a few queries and suggestions:
1. It would be better to change the title to "Incidence of adverse events in drug-naïve children and adolescents treated with antipsychotic drugs: a French multicentre naturalistic study protocol (ETAPE)".
Response: We have taken into account the suggestions of the two reviewers and we have changed the title to: "Incidence of adverse events in antipsychotic-naïve children and adolescents treated with antipsychotic drugs: a French multicenter naturalistic study protocol (ETAPE)".
2. The keywords could include: "children" and "adolescents" instead of "paediatric population" as in the world of child psychiatry usual convention in to search with these words as opposed to "paediatrics" only.
Response: We have changed the keywords as proposed by the reviewer.
3. One of the questions that came to my mind - Why are the authors trying to publish a protocol in

December 2015 when as per the www.clinicaltrials.gov the study was contemplated to be completed in Dec 2015. If most of the study period is over, there is very little value in publishing a protocol at this stage and may in some way make the readers feel that this is a prospective declaration by the authors regarding their primary and secondary analysis even before the study began recruitment of subjects. That was the original justification of publishing protocols early.
Response: The study period will end only in May 2016. The protocol has therefore been updated on the http://www.clinicaltrials.gov. In fact, the French National Agency for Medicines and Health Products Safety (ANSM, n° 2012-004546-15) extended the study for a 6-months period for the reason of an administrative delay for opening of centers. In addition, the Local Ethic Committee gave a favorable opinion in September 2014.
4. Age group: The www.clinicaltrials.gov mention the age of recruitment of patients of the trial number (NCT02007928) to be 13-17. This was published in Dec 2013 after the study was started around July 2013. The current protocol mentions the age group that will be recruited for the same study to be 6 to 18 years. If there is an amendment this should be updated in the Clinical trials registry.
Response: We thank the reviewer for this observation. Unfortunately, the information on http://www.clinicaltrials.gov is incorrect, and we corrected the protocol on clinicaltrials.gov. The age group recruited in the study has always been 6-18 years.
5. Validity of certain instruments in the current age group (6-18 years): If the age group included for the current study is indeed 6-18 years, would the original instruments (e.g. Barne's Akathisia scale) be valid in this age group? Few studies on childhood onset schizophrenia (COS) use these instruments. In these trials, although the onset may be in childhood, the age of the children may be more than 10 years when the children are recruited. The current study is on drug naive children and so may potentially recruit children younger (than most trials on COS etc) and will also include other diagnoses other than COS. Will Barne's Akathisia scale be a valid way to assess akathisia in a 7 year old boy with autism and behaviour problems on Risperidone? As a child psychiatrist I do have my doubts.
Response: Unfortunately, clinical validated scales to assess neuromuscular adverse events are not tailored to the pediatric population. Therefore, its use in children might be limited (see also section 'Limitations of the study' in the manuscript: "The clinical scales used to assess neuromuscular AEs are validated in the adult population which might be a limitation for analyses in young patients."). Nevertheless, these scales help the investigator to diagnose neuromuscular adverse events in children, even if some scales might not be possible to be completed by the investigator in some patients, e. g. patients with severe autistic spectrum disorders.
6. Use of the word 'qualitative': Under measures the authors express that they will be using qualitative measures. In the strict sense of the term, rating scales as Paediatric Adverse Events Rating Scale is a quantitative measure. Please just mention - 'Questionnaires to be used'.
Response: We thank the reviewer for this comment and changed our manuscript.
Measures
Quantitative and qualitative measures are assessed during the study (summary in table 1): clinical parameters (e.g. body weight), laboratory assessment (e.g. blood cholesterol), ECG (e.g. QTc interval), semi-structured interviews to assess main diagnosis at inclusion and after 12-months follow-up (Kiddie-SADS [41], and/or MINI / MINI-Kid [42]), several clinical hetero-assessment with specific rating scale (e.g. the Modified Bush-Francis Catatonia Rating Scale, BFCRS [40 53]), and several self-report questionnaires (e.g. Pediatric Adverse Event Rating Scale, PAERS [47]).
Reviewer: 2
I have a few minor suggestions to the protocol:
- In the title, it would be preferable if they replace "naïve" with "antipsychotic naïve"
Response: We have taken into account the suggestions of the two reviewers and we have changed the title to: "Incidence of adverse events in antipsychotic-naïve children and adolescents treated with antipsychotic drugs: a French multicenter naturalistic study protocol (ETAPE)".
- In Table 1, line 10: Do the authors mean "height" when they say "size"? Please clarify and replace if this is what they mean.
Response: We thank the reviewer for this helpful observation. It is indeed weight, and height, and we

corrected table 1.
- In Table 1, line 20: Please replace “complete blood count” with “full blood count”
Response: We corrected table 1.
- I suspect that the detailed study documents will be in a supplement rather than the main text. Please clarify.
Response: Indeed, the Gantt diagram of ETAPE study and the descriptive assessments during the follow-up are detailed in figure 1 and in table 1. They complete the “Methods and design” section. In addition, the study protocol is accessible on http://www.clinicaltrials.gov (NCT02007928).

VERSION 2 – REVIEW

REVIEWER	Soumitra Shankar Datta Senior Consultant Psychiatrist Department of Palliative Care and Psycho-oncology Tata Medical Centre, Kolkata, India www.tmckolkata.com/tmc/dr_details.php?pid=7&dr_id=24 Visiting Researcher, Institute of Psychiatry, Kings College London Visiting Researcher, Institute of Women's Health, University College London
REVIEW RETURNED	23-Feb-2016

GENERAL COMMENTS	The reviewer completed the checklist but made no further comments.