PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Celecoxib versus placebo as an adjunct to treatment-as-usual in children and youth with obsessive-compulsive disorder: Protocol for a single-site randomized quadruple-blind phase II study
AUTHORS	Westwell-Roper, Clara; Best, John; Elbe, Dean; MacFadden, Megan; Baer, Susan; Tucker, Lori; Au, Antony; Naqqash, Zainab; Lin, Boyee; Lu, Cynthia; Stewart, S. Evelyn

VERSION 1 – REVIEW

REVIEWER	Johnson, Mats Sahlgrenska Academy, Gillberg Neuropsychiatry Centre
REVIEW RETURNED	27-Sep-2021

GENERAL COMMENTS	The research questions and rationale are novel and interesting and study results may have a considerable impact on clinical routines. It is a special strength that the study includes all cases of OCD including PANS/PANDAS cases. The trial is well designed and also adapted to real-life conditions allowing treatment as usual, and novel in using virtual follow-up and labtests at the patient's home clinics, probably facilitating performing the study. The inclusion and exclusion criteria and primary and secondary outcome measures are well chosen. I have a few comments: Page 5. Is a between-group difference in CY-BOCS scores of 2.5 with an SD of 5 really clinically significant? It would be a strength to discuss how this difference would be meaningful in everyday life. If this difference needs to be changed probably a new sample size calculation is needed. It would be a strength to also express the between-group difference as Effect Size. Page 5. Please clarify what "multiply imputed" missing data means? Page 6. It would be interesting to state also the "mg/kg" dosage, since this is often used as guideline in clinical work. Page 6. I would just like to mention that I find it to be a clinically important strength that analysis of meaningful response and of remission is included. Page 7. Is some kind of PANS symptom scale used? Please describe in outcome measure section Page 8. The description of multiple imputation here is complicated and would be improved by clarification/simplification Table 1. Perhaps it should be mentioned here and in the text that patients with PANS/PANDAS are eligible for the trial? What is the rationale for excluding patients with autism? It would be interesting with your considerations here.

REVIEWER	Shalbafan, Mohammadreza Iran University of Medical Sciences, Psychiatry
REVIEW RETURNED	21-Nov-2021

GENERAL COMMENTS	The trial is well-designed and the topic targets one of most novel aspects of psychopharmacology of OCD. Although the manuscript may be improved by considering my comments that are listed below: 1. 'treatment-as-usual' is not clear in the title as well as the abstract. It should be described clearly. 2. All key-words should be selected from MESH. 3. I don`t agree with this sentence as a fact in the abstract: 'Consensus guidelines recommend NSAIDs as an adjunctive approach in adults with obsessive-compulsive disorder (OCD) and in children with acute-onset OCD subtypes.'. It should be softened. 4. Safety of the intervention should be mentioned as one of the main outcomes of the trial. 5. There are three trials report celecoxib efficacy in addition to SSRIs in adult patients with OCD. Please search all databases included Google Scholar again. 6. 'CY-BOCS' should be described in details in the text. 7. Do the patients pay for visits or interventions? What about treatment as usual? 8. There is a typo in 'noepinephrine'.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Mats Johnson, Sahlgrenska Academy, University of Gotheburg
Comments to the Author:
The research questions and rationale are novel and interesting and study results may have a considerable impact on clinical routines. It is a special strength that the study includes all cases of OCD including PANS/PANDAS cases. The trial is well designed and also adapted to real-life conditions allowing treatment as usual, and novel in using virtual follow-up and labtests at the patient's home clinics, probably facilitating performing the study. The inclusion and exclusion criteria and primary and secondary outcome measures are well chosen. I have a few comments:

Page 5. Is a between-group difference in CY-BOCS scores of 2.5 with an SD of 5 really clinically significant? It would be a strength to discuss how this difference would be meaningful in everyday life. If this difference needs to be changed probably a new sample size calculation is needed. It would be a strength to also express the between-group difference as Effect Size.

Thank you for this comment. We agree that a between-group difference of 2.5 is likely of limited clinical significance, but have chosen this as the smallest effect size of interest that we wish to detect. This value represents the difference between scores if an individual with a score of 16 who is eligible to participate in the study were to achieve a score of ≤14, the definition of clinical remission we are using as a secondary outcome to allow for cross-study comparisons (consistent with Storch and colleagues[1]) although we recognize this still represents significant ongoing symptoms and is a suboptimal outcome for any individual patient. Our power calculation could be considered to result in an"overestimate" of the required sample size on this basis, but we feel there is compelling evidence that RCTs are generally too small (see van Zwet and colleagues in the 2021 issue of *Significance* published by the Royal Statistical Society). We aim to maximize our chances of understanding the effect size of this treatment (beyond whether it can be determined to be meaningful or not), and a larger sample size will be helpful with this for providing greater precision (i.e. tighter confidence interval surrounding the estimated difference).

We have clarified on page 5 that the between-group difference equals a Cohen's d effect size of 0.5.

Page 5. Please clarify what "multiply imputed" missing data means?

Thank you for this. Multiple imputation is a statistical technique for handling missing data. We now use the simpler term 'imputed' and note that specific details on the imputation method (now simplified) follow in the Statistical Analysis section.

Page 6. It would be interesting to state also the "mg/kg" dosage, since this is often used as guideline in clinical work.
Thank you. We have added the mg/kg equivalent. Note that the maximum dose is set as per Health Canada requirements even though some published studies in children and youth use higher doses.

Page 6. I would just like to mention that I find it to be a clinically important strength that analysis of meaningful response and of remission is included.
Thank you. While we recognize that there is much debate over the definitions of "response" and "remission" when individuals have ongoing symptoms, we have opted for definitions as commonly used in the OCD literature and described previously according to Storch and colleagues[1].

Page 7. Is some kind of PANS symptom scale used? Please describe in outcome measure section
Thank you for pointing this out. As per Table 2 there is a PANS rating scale included among exploratory outcome measures as part of the Parent/Participant Perspective Questionnaire. We have now added separate description of this scale to the Outcome Measure section.

Page 8. The description of multiple imputation here is complicated and would be improved by clarification/simplification
We have now clarified the description of the multiple imputation procedure, using simpler language as well as removing unnecessary details.

Table 1. Perhaps it should be mentioned here and in the text that patients with PANS/PANDAS are eligible for the trial? What is the rationale for excluding patients with autism? It would be interesting with your considerations here.
These are both very important points – thank you. Patients with ASD have been excluded as there is a previous trial suggesting some benefit of adjunctive celecoxib in this population and the response of ASD-related symptoms might confound outcomes specific for OCD. We have added reference to this finding in the Background section. We have also clarified in the Patient Selection section that participants with PANS or PANDAS who also meet diagnostic criteria for OCD are eligible to participate.

Reviewer: 2
Dr. Mohammadreza Shalbafan, Iran University of Medical Sciences
Comments to the Author:
The trial is well-designed and the topic targets one of most novel aspects of psychopharmacology of OCD. Although the manuscript may be improved by considering my comments that are listed below:
Thank you for your review and comments.

1. 'treatment-as-usual' is not clear in the title as well as the abstract. It should be described clearly.
Thank you for this. Treatment-as-usual refers to the treatment that participants would otherwise be receiving. This will vary among participants according to the choice of the family. We have clarified in the abstract as follows: "Treatments will be added to participants' routine clinical care, which will not change over the course of the study."

We have also added a sentence to the Study Setting section specifying that participants will continue to receive treatment-as-usual from their regular health care providers, which will not change as a result of participation in this study.

Please note that the Patient Selection section also describes possibilities for treatment-as-usual and we now have added the phrase "according to their routine clinical care":
Participants may be receiving concurrent pharmacotherapy or psychotherapy according to their routine clinical care, constituting "treatment-as-usual" as long as there have been no changes in the preceding 4 weeks and during the study period.

2. All key-words should be selected from MESH.
Thank you for this comment. The keywords we had initially selected have now been rephrased to ensure they are consistent with MESH headings (e.g. non-steroidal anti-inflammatory drug has now been chanted to “anti-inflammatory agents, non-steroidal”). We have added several additional keywords in place of the use of “pediatric” as an adjective, all of which are MESH terms: Obsessive-compulsive disorder; anti-inflammatory agents, non-steroidal; cyclooxygenase inhibitors; randomized controlled trial; child; adolescent; Pediatrics; child health

3. I don`t agree with this sentence as a fact in the abstract: ‘Consensus guidelines recommend NSAIDs as an adjunctive approach in adults with obsessive-compulsive disorder (OCD) and in children with acute-onset OCD subtypes.’. It should be softened.
Thank you for this comment. This statement refers in particular to the 2014 Canadian guideline for management of anxiety disorders including OCD, in which celecoxib is listed as a third-line adjunct, and to the Frankovich *et al.* 2017 guidelines for management of PANS/PANDAS in which it is suggested as a first-line immune-modulating agent. We agree that in an abstract with no citations softening is warranted and have changed it as follows: “Consensus guidelines suggest NSAIDs as a *possible* adjunctive approach…”

4. Safety of the intervention should be mentioned as one of the main outcomes of the trial.
Thank you. Difference between arms with respect to adverse event frequency is defined as a *secondary outcome* of the study, as described in the Outcome Parameters and Statistical Analyses section. The abstract also describes secondary outcomes including “proportion of participants reporting adverse events possibly or probably related to the study intervention.” Given that multiple studies in larger groups of children and youth have previously evaluated celecoxib safety with greater power to do so, we feel that a primary efficacy outcome is most appropriate here (and the one on which the study power is based), with safety endpoints included among the other outcomes and descriptive analyses. As described in the Outcome Measures section, adverse events will be systematically assessed at study visits and using participant electronic diaries. To highlight the importance of safety as well as efficacy end-points, we have now added a sentence to the first paragraph to further emphasize safety outcomes.

5. There are three trials report celecoxib efficacy in addition to SSRIs in adult patients with OCD. Please search all databases included Google Scholar again.
Thank you. It appears that a third paper was published following submission of this manuscript, and is not indexed on PubMed or included in a clinical trial registry. We have now added this, assuming the following is the reference to which the reviewer alludes:

Shahini, Sh., Talaei, A., Shalbafan, M., Faridhosseini, F., & Ziaee, M. (2021). Effects of Celecoxib Adjunct to Selective Serotonin Reuptake Inhibitors on Obsessive-compulsive. Basic and Clinical Neuroscience, 12(4), 489-498.

6. ‘CY-BOCS’ should be described in details in the text.
Thank you for pointing out the need for more detail. The Outcome measures section describes the CY-BOCS and also references the original study for further information. We have now added some clarifying information with more details of the scale.

7. Do the patients pay for visits or interventions? What about treatment as usual?
There is no cost to participants for participation in this study, and we have now added this statement to the “Participant schedule and follow-up” section. Treatment-as-usual is not provided as part of the study but by participants’ regular care providers (see emphasis added to text above).

8. There is a typo in ‘noepinephrine’.
Thank you – this has been fixed.

References
1. Storch EA, Lewin AB, De Nadai AS, et al. Defining treatment response and remission in obsessive-compulsive disorder: a signal detection analysis of the Children's Yale-Brown Obsessive

Compulsive Scale. *J Am Acad Child Adolesc Psychiatry* 2010;49(7):708-17. doi: 10.1016/j.jaac.2010.04.005 [published Online First: 2010/07/09]
2. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry* 1989;46(11):1006-11.
3. Rapp AM, Bergman RL, Piacentini J, et al. Evidence-Based Assessment of Obsessive-Compulsive Disorder. *J Cent Nerv Syst Dis* 2016;8:13-29. doi: 10.4137/JCNSD.S38359
4. Storch EA, McGuire JF, Wu MS, et al. Development and Psychometric Evaluation of the Children's Yale-Brown Obsessive-Compulsive Scale Second Edition. *J Am Acad Child Adolesc Psychiatry* 2019;58(1):92-98. doi: 10.1016/j.jaac.2018.05.029 [published Online First: 2018/12/24]

VERSION 2 – REVIEW

REVIEWER	Johnson, Mats Sahlgrenska Academy, Gillberg Neuropsychiatry Centre
REVIEW RETURNED	02-Jan-2022

GENERAL COMMENTS	The authors have responded to all my comments and made appropriate clarifications. I have only one new comment: It would be a strength to add in the ethics section that all participants/caregivers provide informed consent to be included in the study.

REVIEWER	Shalbafan, Mohammadreza Iran University of Medical Sciences, Psychiatry
REVIEW RETURNED	29-Dec-2021

GENERAL COMMENTS	Thank you for sending the revised manuscript for review. All of my comments have been addressed appropriately.