PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Pharmacological Emergency management of Agitation in Children and Young people: Protocol for a randomised controlled trial of Oral medication (PEAChY-O)
AUTHORS	Bourke, Elyssia; Borland, Meredith; Kochar, Amit; George, Shane; Shellshear, Deborah; Jani, Shefali; Perkins, Kent; Tham, Doris; Gordon, Michael; Klein, Kate; Prakash, Chidambaram; Lee, Katherine; Davidson, Andrew; Knott, Jonathan C.; Craig, Simon; Babl, Franz

VERSION 1 – REVIEW

REVIEWER	Silva, Elisabete Pereira Universidade Federal de Pernambuco, Materno-Infantil
REVIEW RETURNED	22-Oct-2022

GENERAL COMMENTS	The study contributes to the evaluation of the use of oral medication for sedation of children and adolescents with acute severe behavioral disturbance, in emergency departments. I suggest that in the SPIRIT Checklist the page numbers are reviewed because I was not able to locate some topics by the cited numbers. ABSTRACT It is well structured and written in a concise and easy-to-read form, highlighting the main points of the article. INTRODUCTION It presents the study problem in a consistent and well-structured manner, placing the significance of the study based on relevant and updated literature and defining the objectives of the study. METHODS They were described in a detailed and clear way.

	DISCUSSION The authors discuss the strengths and limitations of the study adequately. REFERENCES The references are updated and organized according to the journal's rules.

REVIEWER	Chan, Esther University of Hong Kong, Pharmacology and Pharmacy
REVIEW RETURNED	05-Dec-2022

GENERAL COMMENTS	Nice to see a sedation study in this important patient group. Diverse and experienced clinician researchers among the research team; study conducted on behalf of the PREDICT research network and was reviewed and supported by the NHMRC. Assuming it will be oral olanzapine tablets (and not oro-dispersable wafers), wonder if it may be possible to do a double-blind, rather than open label but would involve concealing the appearance of the two types of tablets. If indeed not possible, it will be important for the nurse recording the scores to be a different nurse to the one who had administered the open-label drug due to the potentially subjective nature of scoring.

REVIEWER	Isbister, Geoff University of Newcastle, Clinical Toxicology Research Group
REVIEW RETURNED	09-Dec-2022

GENERAL COMMENTS	These are both very good study protocols. I have a couple of concerns, one that needs to be addressed by a statistician. However, both of these studies have started, so these concerns cannot be addressed, since the study has commenced - so this is more about the design, and not the publication of the design. 1. I may have missed it but I cant see how the two studies work together. As the authors describe, oral meds are attempted prior to IM - however, both studies have the same inclusion criteria for severe ABD. How will this work? How does a clinician decide which study to recruit the patient two. Does giving oral medication exclude the patient from the IM study. THis is unclear, and I got quite confused at first until I realised they are two studies, with essentially the same design, but one oral, one IM. 2. My second concern is about the design of the study. What is the rationale for a superiority study when undertaking a comparison RCT with little previous data and no placebo randomised controlled trial. And why are both superior studies of olanzapine. So there are actually 3 possible outcomes - olanzapine is superior, they are equally effective (probably the most likely outcome, particularly for the oral study), diazepam or droperidol is superior. How have the investigators accounted for this. I would have thought a more appropriate design is a non-inferiority study, that olanzapine is just as effective as either diazepam or droperidol.

	Finally, if the treatments are shown to be similar, how can we be sure that they are just equally ineffective ?

REVIEWER	Franklin, Donna Griffith University Menzies Health Institute Queensland, Children's Critical Care Research Group
REVIEW RETURNED	12-Dec-2022

GENERAL COMMENTS	ASBD is an increasing problem for clinicians working in the ED. The authors are making (correctly) the claim that current treatment for ASBD if escalated behaviour is observed, and non-pharmacological strategies are working then they escalate to oral medication. However limited evidence exists in the paediatric population. This is important paediatric data to be obtained. This manuscript outlines the protocol of an important study that aims to determine whether a single dose of oral olanzapine is superior to a single dose of oral diazepam in successfully sedating young people presenting with ASBD who require oral medication. Hypothesis The authors aim to demonstrate that single dose of oral olanzapine is superior to a single dose of oral diazepam. It is not clear enough why the authors hypothesise that olanzapine could confer superiority. Design Multi-centre, open-labelled RCT, which uses the superiority hypothesis. This is an adequate approach. Patient and public involvement The precise process on how the public has been engaged should be described. Working groups, parents and/or children, clinicians etc. I am suggesting a more detailed description as this has obviously occurred. Additionally, are these parents/consumers a continued CAG for the study. If so, this should be outlined. Setting A large representation of tertiary Paed ED's. Suggest using the title Settings and Participants or separate the two headers, one of the settings and one for the participants. The way it reads, participant information occurs under the Setting Header. Possibly create a separate section for Analysis tools, where you describe the tools used for assessment of the primary outcome. This will further break that section down into relevant specific parts. Outcome definitions The primary outcome is well defined and robust. However, the primary outcome should be defined from time of application of the intervention to effect (1 hour post application), whereas the efficacy outcome should be time from randomisation to administering of the intervention. I understand the investigators want to test how rapidly the intervention is applied. This may confuse the primary outcome. The primary outcome should be 1 hour after application of the drug. The efficacy outcome should be the time to deliver the drug. There may be logistic problems to achieve this, and this would allow a better distinction between effect of the drug vs efficiency of the process.

	Randomisation Explain in more detail the randomisation process, block sizes, stratification per centre, age or more likely weight, SAT Score, 1:1 allocation? Why not have your starting point once the drug has been applied rather than randomisation time as this would be more relevant to the drug efficiency and not system efficiency. Missing is the information on how many patients are expected per site (historical data to demonstrate that the number of patients can be recruited). Data collection Adequately described. TSC and DSMB mentioned, however should the DSMB not meet after a certain number of patients enrolled? Statistical approach Not sure if a two-sided test is the correct approach for a superiority trial. A two-sided test would allow to assess both superiority and inferiority.

VERSION 1 – AUTHOR RESPONSE

Reviewer comments	
Reviewer One: Dr. Elisabete Pereira Silva, Universidade Federal de Pernambuco	
The study contributes to the evaluation of the use of oral medication for sedation of children and adolescents with acute severe behavioral disturbance, in emergency departments. I suggest that in the SPIRIT Checklist the page numbers are reviewed because I was not able to locate some topics by the cited numbers.	The page numbers have been reviewed and corrected in the SPIRIT Checklist.
ABSTRACT It is well structured and written in a concise and easy-to-read form, highlighting the main points of the article. INTRODUCTION It presents the study problem in a consistent and well-structured manner, placing the significance of the study based on relevant and updated literature and defining the objectives of the study. METHODS They were described in a detailed and clear way. DISCUSSION The authors discuss the strengths and limitations of the study adequately. REFERENCES The references are updated and organized according to the journal's rules.	Thanks for the positive comments. No response required from the authorship team.

Reviewer Two: Dr. Esther Chan, University of Hong Kong	
Nice to see a sedation study in this important patient group. Diverse and experienced clinician researchers among the research team; study conducted on behalf of the PREDICT research network and was reviewed and supported by the NHMRC.	Thank you Dr Chan for the positive comments.
Assuming it will be oral olanzapine tablets (and not oro-dispersable wafers), wonder if it may be possible to do a double-blind, rather than open label but would involve concealing the appearance of the two types of tablets. If indeed not possible, it will be important for the nurse recording the scores to be a different nurse to the one who had administered the open-label drug due to the potentially subjective nature of scoring.	We are using oro-dispersable wafers as this is the standard formulation used in the Australasian context. We did consider using a double-placebo design when designing the trial, but we decided that it would be too challenging logistically as it would have required the agitated young person to take two interventions – one tablet and one wafer, one of which would be active and one placebo. As you are likely aware, it is hard enough in this cohort to get patients to take one intervention – so we decided adding an additional intervention (and the risk of them then just taking the placebo and no active tablet – or taking neither) was not feasible. In the vast majority of instances, although nursing staff are listed as being able to be involved in the scoring, it is a doctor who is undertaking the SAT scoring. This may be the treating doctor or it may be a different doctor working in the department, both of whom would be unaware of the treatment assignment. In only a small proportion of cases it is the same nurse conducting the randomisation and assessing the outcome. Given the objective nature of the score, and that it is very clear as to what constitutes a +1 or a +2 etc; coupled with the pragmatic nature of the study and staffing limitations, we decided not to stipulate that another nurse needs to complete the scoring. This has been noted as a limitation in the protocol paper: Our study design has a number of limitations. The trial is open-label. This was necessary to ensure that any AEs that occurred could be recognised and rapidly acted upon. This also means that clinical staff who are determining the SAT score will be aware of the study drug allocation. It will also be noted as a limitation when the results of the study are published.
Reviewer Three: Dr. Geoff Isbister, University of Newcastle	
These are both very good study protocols. I have a couple of concerns, one that needs to be addressed by a statistician. However, both of these studies have started, so these concerns	Thank you Dr Isbister for your comments. We have provided responses to these queries below, which have been formulated in consultation with our trial statistician (Prof Katherine Lee) who has extensive

cannot be addressed, since the study has commenced - so this is more about the design, and not the publication of the design. 1. I may have missed it but I cant see how the two studies work together. As the authors describe, oral meds are attempted prior to IM - however, both studies have the same inclusion criteria for severe ABD. How will this work? How does a clinician decide which study to recruit the patient two. Does giving oral medication exclude the patient from the IM study. Tspan style="font-family:Arial; color:#242424; background-color:#ffffff">his is unclear, and I got quite confused at first until I realised they are two studies, with essentially the same design, but one oral, one IM.	trial experience, and was also involved in the conception of both of these studies. We apologise for the confusion created through having two separate study protocols in which the majority of aspects are indeed similar. We have explained the rationale for having these as independent studies in the response to the Editor. Importantly there are two groups of patients in whom we are trying to determine the most effective medication choice – those who are deemed by the ED clinician as likely to accept oral medication (who get enrolled into PEAChY-O) and those who the ED clinician assesses as unwilling or unable to accept oral medication, therefore requiring parenteral medication (who get enrolled into PEAChY-M). This difference in the population of the two studies is reflected in the inclusion criteria for the two trials. In practice, when a young person presents with ASBD, the treating clinician assess them to determine whether they are likely to accept oral medication or require parenteral medication. The former are then enrolled into PEAChY-O. Yes, once a patient has been enrolled into PEAChY-O they are then ineligible for PEAChY-M. Again we discussed this in depth when planning the two studies. For both studies, the 'start time' for the definition of the primary and secondary outcomes is randomisation, as we are aiming to assess effectiveness of the medications as the primary objective i.e. the effect of being offered one intervention over the other. If we allowed PEAChY-O participants to subsequently be enrolled/randomised into PEAChY-M then they would have 2 different start times for each trial. We thought this would cause a lot of confusion when collecting the outcomes for both of the studies and could jeopardise the integrity of the data for both. Given this, we thought it would be much cleaner to stipulate that once a participant is enrolled into PEAChY-O, regardless of whether they take the medication or not, they remain enrolled in PEAChY-O (intention to treat approach) and are ineligible for PEAChY-M.
2. My second concern is about the design of the study. What is the rationale for a superiority study when undertaking a comparison RCT with little previous data and no placebo randomised controlled trial. And why are both superior studies of olanzapine. So there are actually 3 possible outcomes - olanzapine is superior, they are equally effective (probably the most likely outcome, particularly for the oral study), diazepam or droperidol is superior. How have	We acknowledge your concern and agree that the study design is an important decision, which is particularly challenging in the face of limited data. The reason we selected a superiority design is that we want to identify the best (i.e.: superior) agent for both oral and IM sedation for young people that is both safe and effective. We decided to undertake a comparative effectiveness trial due to the physical & psychological risk posed by this population - we do not believe it would be ethical to

the investigators accounted for this. I would have thought a more appropriate design is a non-inferiority study, that olanzapine is just as effective as either diazepam or droperidol. Finally, if the treatments are shown to be similar, how can we be sure that they are just equally ineffective ?	undertake a placebo-controlled trial due to these concerns. We agree with your point that there is currently not a robust base of retrospective or prospective literature in this population, which is why we undertook an Australian survey of emergency clinicians caring for young people with behavioural disturbance to determine what agents they were using and what agents they would like to see used in a comparative effectiveness trial, and what they thought the relative effectiveness of the interventions would be. This survey, in combination with discussions with the trial steering committee and our psychiatric colleagues assisted in our determination to hypothesize oral olanzapine and IM olanzapine as 'superior' agents in the two studies. As PEAChY-O and PEAChY-M are separate studies in separate populations, we do not account for the fact that we use olanzapine in both studies. These two studies will be analysed completely separately. As with any study, we understand that these studies may not provide the definitive answer as the best agent for paediatric ASBD, but as the first randomised controlled trials in these populations they should at least provide an initial evidence base that we can take forward into future studies.
Dr. Donna Franklin, Griffith University Menzies Health Institute Queensland	
ASBD is an increasing problem for clinicians working in the ED. The authors are making (correctly) the claim that current treatment for ASBD if escalated behaviour is observed, and non-pharmacological strategies are working then they escalate to oral medication. However limited evidence exists in the paediatric population. This is important paediatric data to be obtained. This manuscript outlines the protocol of an important study that aims to determine whether a single dose of oral olanzapine is superior to a single dose of oral diazepam in successfully sedating young people presenting with ASBD who require oral medication. Hypothesis The authors aim to demonstrate that single dose of oral olanzapine is superior to a single dose of oral diazepam. It is not clear enough why the authors hypothesise that olanzapine could confer superiority.	Thank you, Dr Franklin, for your comprehensive review of our two protocol papers. As per our response to Reviewer 3, the investigators chose to test this hypothesis based on expert opinion, clinical practice guidelines and results obtained from emergency physicians practice preferences in an Australian survey undertaken by the research team. Considering the currently lacking evidence base and preferences from clinicians to have a 'first choice' medication option, the research team determined that undertaking a superiority trial was the most appropriate approach.
Design Multi-centre, open-labelled RCT, which uses the	No response required from the authorship team.

superiority hypothesis. This is an adequate approach	
Patient and public involvement The precise process on how the public has been engaged should be described. Working groups, parents and/or children, clinicians etc. I am suggesting a more detailed description as this has obviously occurred. Additionally, are these parents/consumers a continued CAG for the study. If so, this should be outlined.	In regards to the engagement process, the parent consumers are the only group (outside of the trial steering committee – all of whom are authors) who have been engaged in the design of the study protocol. There were not specific working groups or other clinicians involved in the study design process. The parent consumers will have ongoing involvement with the study, including yearly updates, the opportunity to review and comment on the results and to be involved in the knowledge translation process. We have added an additional sentence to outline this process in the manuscript: These parent consumers will have ongoing involvement throughout the life of the study. Regular updates will be provided in a written format whilst data collection is being undertaken. Once the study results are available, these will be provided to parent consumers allowing them a chance to comment on the findings which will be incorporated into any publications or presentations. They will also be involved in the knowledge translation of the results of the study.
Setting A large representation of tertiary Paed ED's. Suggest using the title Settings and Participants or separate the two headers, one of the settings and one for the participants. The way it reads, participant information occurs under the Setting Header.	We have updated the title of this section as suggested to read "Setting and participants"
Possibly create a separate section for Analysis tools, where you describe the tools used for assessment of the primary outcome. This will further break that section down into relevant specific parts.	We have slightly modified the order of the text in the 'setting and participants' section which has allowed us to include a sub-heading 'The Sedation Assessment Tool' and to ensure clarity we have added an additional sub-heading below this 'Inclusion and exclusion criteria'
Outcome definitions The primary outcome is well defined and robust. However, the primary outcome should be defined from time of application of the intervention to effect (1 hour post application), whereas the efficacy outcome should be time from randomisation to administering of the intervention. I understand the investigators want to test how rapidly the intervention is applied. This may confuse the primary outcome. The primary outcome should be 1 hour after application of the drug. The efficacy outcome should be the time to deliver the drug. There	This was an issue that was discussed extensively during the study design phase and we (and in particular our biostatistician) felt strongly that the time should start from randomisation. This was also requested by our independent DSMB who met to review the study protocols prior to the trial commencing. We want to confirm that what we are measuring as our primary outcome is the effectiveness of the medication (how well it works if offered) as this is our primary research question. To determine this, we needed to use the time of randomisation as the start time. We are also assessing efficacy (how well it works if actually taken) as a secondary outcome of the study,

may be logistic problems to achieve this, and this would allow a better distinction between effect of the drug vs efficiency of the process.	as well as the time from randomisation to administration of the intervention. In PEAChY-O, olanzapine wafer is a yellow tablet dispensed from drug room stock, diazepam is a white tablet which is a restricted drug held in a locked cabinet that needs to be checked out by two staff members. In PEAChY-M, olanzapine is a yellow liquid and droperidol is a clear liquid. Therefore, there are system differences as well as noticeable physical differences between the trial interventions which may mean that participants would need to 'wait' longer to receive them, or be less (or more) willing to take them. If we were to take the start time as the time of application rather than randomisation, this could induce confounding, particularly if there is difference in the time to receiving the intervention between the two arms, as it is no longer formally a randomised comparison. It would also mean that there would be no start time for those who never received the medication which would be problematic for defining our outcome. For all of these reasons, we decided that the start time should be the time of randomisation.
Randomisation Explain in more detail the randomisation process, block sizes, stratification per centre, age or more likely weight, SAT Score, 1:1 allocation?	We have updated this paragraph to provide additional information regarding the randomisation. We are only stratifying by centre; there is no stratification by age, weight or SAT score. We now provide the following information about the randomisation process: Participants will be randomised in a 1:1 ratio between olanzapine and diazepam. The randomisation schedule will be computer generated by an independent statistician in the Clinical Epidemiology and Biostatistics Unit (CEBU) at the MCRI using block randomisation with variable block size (with blocks of size 2, 4 and 6), stratified by site (10 strata). Treatment allocation will be via opaque, sealed envelopes.
Why not have your starting point once the drug has been applied rather than randomisation time as this would be more relevant to the drug efficiency and not system efficiency.	As per our response to the previous comments the research question of interest in this study is regarding the comparative effectiveness of the interventions (i.e. the offering of the interventions) rather than efficacy (i.e. the taking of the interventions). This coupled with the other reasons mentioned above is why we have chosen randomisation as our starting point.
Missing is the information on how many patients are expected per site (historical data to demonstrate that the number of patients can be recruited).	The data relating to this is not published, but from audit data we thought it would be feasible to recruit 50 patients per study per site. With both studies now recruiting for 12 months, we have discovered that this may not be able to be achieved within the study funding timeframe. We have therefore expanded the study to ten sites. We have

	added an additional sentence to 'setting and participants' as below: We aim to recruit 35 participants per site between October 2021 and December 2023, to achieve our sample size of 348 participants. We believe this is feasible within the specified timeframe based on our review of non-published audit data.
Data collection Adequately described	No response required from the authorship team.
TSC and DSMB mentioned, however should the DSMB not meet after a certain number of patients enrolled?	The independent DSMB decided to meet after a specified timeframe rather than a specific number of patients and this has been outlined in our DSMB charter. This is fairly common in practice.
Statistical approach Not sure if a two-sided test is the correct approach for a superiority trial. A two-sided test would allow to assess both superiority and inferiority.	Using a two-sided test is standard practice and aligns with presenting a 95% confidence interval, which is in line with standard practice and journal and reader expectations. If we changed this to a one-sided test with alpha=5%, this would require presenting 90% confidence intervals reducing the certainty of the results and would likely result in criticism. When we present the results from this study, they will be interpreted for what they are and prominence given to the estimate and confidence intervals, rather than focussing on the p-value in line with modern statistical thinking.

VERSION 2 – REVIEW

REVIEWER	Isbister, Geoff University of Newcastle, Clinical Toxicology Research Group
REVIEW RETURNED	08-Jan-2023

GENERAL COMMENTS	I do not believe the authors have answered the question of superiority versus inferiority. They have done this based on I suspect the investigators beliefs and surveys of clinicians that one agent is better than the other. I simply do not believe there is any evidence to support this. However, clearly this is not going to change, so I have no further comments.

REVIEWER	Franklin, Donna Griffith University Menzies Health Institute Queensland, Children's Critical Care Research Group
REVIEW RETURNED	24-Jan-2023

GENERAL COMMENTS	Happy with the minor changes made to the original paper. Recognising that there remains two papers which are both similar in format and words with a slight difference in drugs (oral vs IM), if they are to be published as two papers then I am happy with the latest revision.