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)	Can children swallow tablets? Outcome data from a feasibility study to assess the acceptability of different sized placebo tablets in children (Creating Acceptable Tablets - CAT)
AUTHORS	Bracken, Louise; McDonough, Emma; Ashleigh, Samantha; Wilson, Fiona; Shakeshaft, Joanne; Ohia, Udeme; Mistry, Punam; Jones, Huw; Kanji, Nazim; Liu, Fang; Peak, Matthew

VERSION 1 – REVIEW

REVIEWER	Dr. Michael Rieder Department of Paediatrics University of Western Ontario London, Ontario Canada
REVIEW RETURNED	28-Jan-2020

GENERAL COMMENTS	This manuscript describes a study exploring the feasibility of dosing children with a solid dosage form by studying the acceptability of a number of different sized placebo tablets in children aged 4 to 12 years who were patients in a hospital system in northern England. The authors have demonstrated feasibility in dosing for most of the children studied. They have also demonstrated important feasibility issues related to recruitment, i.e. the relative ease of recruiting healthy volunteers and the great difficulty in recruiting from patients, an issue that is very familiar to this reviewer from previous studies and personal experience. The area of appropriate child-friendly paediatric formulations has been a smouldering topic for some time with little work being done until fairly recently. It has been identified as an issue limiting therapy in a number of jurisdictions and thus this is both timely and important for children's care. The group undertaking this work include a number of well regarded and highly productive investigators in paediatric drug therapy and this work is centered in a major British children's hospital system. The methodology used is robust, reliable and valid. The data is presented in considerable and in the view of this reviewer appropriate detail. The conclusions are data driven and the limitations of the study are acknowledged. The finding of relative better performance for larger tablets is interesting and clearly needs further exploration. The details as to volume of fluid needed are helpful guides to further research.

	There are several minor issues that could be explored. Were the research staff trained as to a uniform standard for grading the facial expressions? The children in the study in some cases commented on taste. Did the tablets have a taste, i.e. were any flavouring agents added at all or was the taste commented on a subjective reflection of what was probably a very bland formulation? While the numbers are small, did the fact that 23% of younger children were not tablet-naive impact on their ability to swallow tablets? While this study may not have the numbers to address this, it is certainly a topic of much pragmatic debate among clinicians.

REVIEWER	Toine Egberts Utrecht University and University Medical Center Utrecht, The Netherlands
REVIEW RETURNED	11-Feb-2020

GENERAL COMMENTS	This is an interesting study on a relevant and understudied subject: acceptability and tolerability of tablets by children. Major points: 1) Design: The authors call this a feasibility study, which I do not entirely understand. I would consider a study on approximately 10 subjects as a pilot or feasibility study, but not the current study on 55 subjects. Especially, because I know from own experience how difficult it can be to recruit 55 participants for a study like this. I suggest to remove the word 'feasibility' throughout the manuscript. In line with this comment I would skip the recruitment part from the methiods section (it is also not mentioned in the aims), but to address this in the discussion. 2) Consistency of outcomes: the authors are inconsistent in mentioning the measured outcomes and findings thereon. For example - The title and objective are not fully aligned with the outcomes measured in the study; the title mentions swallowability and acceptability, but the authors measure more outcomes - Abstract - results and conclusion: not all outcomes are reported - Methods: to me it is not clear which of the four outcomes (swallowability, acceptability, water, taste) is measured by the researcher observation. I suggest to restructure and define for each of the four outcomes how it is measured by researcher and/or patient. It might be that the authors reformulate the outcomes.

	- The aforementioned comment also needs restructuring the results section. I really miss a table where the tablet size is in the row and the four outcomes in the columns. 3) The study includes 6/8/10 mm tablets. Several studies included 2/4 mm tablets. This limitation should be mentioned in the discussion. 4) The tablets were not administered in a random order but in the order 6->8->10 mm. The authors should discuss how this might influence the findings. Minor points: 1) Abstract - design and setting: I suggest to formulate more clearly that each participant had to swallow all three tablets. In addition, not all outcomes (researcher and patient) are mentioned here. Please make complete. 2) The following reference is more appropriate than reference 8: van Riet-Nales DA, de Neef BJ, Schobben AF, Ferreira JA, Egberts TC, Rademaker CM. Acceptability of different oral formulations in infants and preschool children. Arch Dis Child. 2013 Sep;98(9):725-31. doi: 10.1136/archdischild-2012-303303. 3) replace 'volume' by 'volume of water consumed" 4) I suggest to replace the subheading 'data collection' in the methods section, by 'outcomes' 5) Table 1: I suggest to remove the column cumulative percent.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1's comments	**Response**
There are several minor issues that could be explored. Were the research staff trained as to a uniform standard for grading the facial expressions?	PM had previous experience of using these methods in the same population group and had published this work (Ref 5). She provided training to all research staff before the study commenced. All research staff watched a training video and completed an

	assessment of facial expressions which was compared for accuracy of detecting the different expressions. Further training was provided for the other team members as needed. This has now been included in the methods. Changes made to paper accordingly (See Staff training / page 5, clean version).
The children in the study in some cases commented on taste. Did the tablets have a taste, i.e. were any flavouring agents added at all or was the taste commented on a subjective reflection of what was probably a very bland formulation?	There were no flavouring agents added to the formulation and the placebo tablets were film coated (Opadry) which is designed to taste mask. This is a bland / neutral formulation which the children were commenting on. Taste was assessed using 5 point hedonic scale – 'very good' to 'very bad'. In the question "what would be most important to you?" options included taste and after taste. Under the question "Anything else about the sample" – some participants also mentioned taste at this point. This should become clearer now that we have separated out how each of the different outcomes has been assessed within the revised manuscript. Changes made to paper accordingly (See Interventions / page 5 and Assessment of Taste / page 7, clean version).
While the numbers are small, did the fact that 23% of younger children were not tablet-naive impact on their ability to swallow tablets? While this study may not have the numbers to address this, it is certainly a topic of much pragmatic debate among clinicians.	In total, 14/55 (25%) participants were unable to swallow at least one of the three sized tablets: of these 13 participants were 4-8 years old and one participant was 9-12 years old. The proportion of tablet naïve participants was 77% in the 4-8 years old group and 16% in the 9-12 years old group. 11/14 (79%) participants who were not able to swallow at least one of the tablets were tablet-naïve and these were all in the younger age group. These preliminary data suggest that there may be an association between tablet naivety and the ability to swallow a tablet.

	Changes made to paper accordingly (See Discussion / page 15, clean version)
Reviewer's 2 comments	
Major points:	
1) Design: The authors call this a feasibility study, which I do not entirely understand. I would consider a study on approximately 10 subjects as a pilot or feasibility study, but not the current study on 55 subjects. Especially, because I know from own experience how difficult it can be to recruit 55 participants for a study like this. I suggest to remove the word 'feasibility' throughout the manuscript. In line with this comment I would skip the recruitment part from the methods section (it is also not mentioned in the aims), but to address this in the discussion.	Thank you for raising this. We have used the definition of feasibility study as in the paper by Arain et al. which describes best practice guidance for such studies (added in as an additional reference, Ref 12). This is a feasibility study as it is seeking to obtain estimates of key parameters (referred to in Introduction, page 4 – clean version) needed to design a definitive trial. In the Arain paper, the median sample size for feasibility studies acquired through a structured literature review was n = 125. One important aspect of the feasibility study was to obtain estimates of recruitment rates and consent rates in the hospital setting. We therefore believe that these data are important to report as they show that a definitive trial is not feasible in this setting. Changes made to paper accordingly (See Introduction / page 4, clean version)
2) Consistency of outcomes: the authors are inconsistent in mentioning the measured outcomes and findings thereon. For example - The title and objective are not fully aligned with the outcomes measured in the study; the title mentions swallowability and acceptability, but the authors measure more outcomes - Abstract - results and conclusion: not all outcomes are reported - Methods: to me it is not clear which of the four outcomes (swallowability, acceptability, water, taste) is measured by the researcher observation. I suggest to restructure and define for each of the four outcomes how it is measured by researcher and/or patient. It might be that the authors reformulate the outcomes.	Sections within the title, abstract, methods and results have been rewritten and now include all outcomes measured in the study. This clarifies which outcomes were measured by the researcher and/or reported by the participant as per below (Refer to page 6/7, clean version): **Swallowability** Participant: Hedonic scale and open question on questionnaire. Researcher: Asked about general swallowability. **Volume**

- The aforementioned comment also needs restructuring the results section. I really miss a table where the tablet size is in the row and the four outcomes in the columns.	Participant: Hedonic scale in terms of rating amount of water needed to swallow each tablet. Researcher: Measured the volume of water consumed. **Acceptability** Participant: Hedonic scale Researcher: Behavioural score was calculated based on facial expressions / behaviours observed by the researcher at time of administration and asked about general acceptability of each tablet. **Taste** Participant: Hedonic scale and open question per below. **Other questions on participant questionnaire** Willingness to take tablets? Tablet taking history? Which most important – taste, smell, tablet size, taste left in mouth, texture? Tell us anything else about this sample?
3) The study includes 6/8/10 mm tablets. Several studies included 2/4 mm tablets. This limitation should be mentioned in the discussion.	This study specifically focuses on tablets which are larger than mini-tablets (greater than 5mm), and which are currently much more widely used in paediatric practice than mini-tablets. We also acknowledge that mini-tablets were not included in this study as we chose not to reproduce the published swallowability studies of mini-tablets in the infant and child population (Klingmann et al). This has been made clearer in the revised manuscript within the discussion. New reference added – ref 13.

	Changes made to paper accordingly (See Discussion / page 14, clean version).
4) The tablets were not administered in a random order but in the order 6->8->10 mm. The authors should discuss how this might influence the findings.	We acknowledge not having randomised the size of tablets was a limitation; however, this was done because of the concerns of choking with larger tablets for those patients who had no previous experience of swallowing tablets (see discussion last paragraph). We also discussed this specific point with a group of children and young people at the study design phase and the methodology used was based on their feedback. This was a feasibility study for a larger randomised trial and we asked children if they were willing to participate in a future study in which the order of tablet size administration would be randomised. Based on the feedback from participants, we would include randomization of tablet size administration order in future trial. This is also mentioned within the discussion. Changes made to paper accordingly (See Article summary - limitation of study bullet points / page 2 and Discussion / page 16, clean version)
Minor points:	
1) Abstract - design and setting: I suggest to formulate more clearly that each participant had to swallow all three tablets. In addition, not all outcomes (researcher and patient) are mentioned here. Please make complete.	We have amended the sentence in the Design and Setting section in the abstract to 'Participants aged 4-12 years were asked to swallow **each of** the three different sized placebo tablets; 6mm, 8mm and 10mm, smallest to largest'. Children were given the opportunity to swallow all three samples but could stop at any point they wished. Some stopped after first, some after the second. Some attempted all three but did not succeed. We have also amended the Design and Setting section in the abstract to include reference to all the outcomes assessed (researcher and patient).

	Changes made to paper accordingly (See Abstract / page 1, clean version).
2) The following reference is more appropriate than reference 8: van Riet-Nales DA, de Neef BJ, Schobben AF, Ferreira JA, Egberts TC, Rademaker CM. Acceptability of different oral formulations in infants and preschool children. Arch Dis Child. 2013 Sep;98(9):725-31. doi: 10.1136/archdischild-2012-303303.	Reference 8 has been replaced with this reference on the revised manuscript. Changes made to paper accordingly (See References / page 18-19, clean version)
3) replace 'volume' by 'volume of water consumed"	Change completed throughout the revised manuscript.
4) I suggest to replace the subheading 'data collection' in the methods section, by 'outcomes'	Done. (See Outcomes / page 6, clean version)
5) Table 1: I suggest to remove the column cumulative percent.	This actually refers to Table 2 and it has been amended accordingly. This change cannot be tracked on the revised manuscript (See Results – Table 2 / page 10, clean version).

VERSION 2 – REVIEW

REVIEWER	Dr. Michael Rieder University of Western Ontario Canada
REVIEW RETURNED	17-Apr-2020

GENERAL COMMENTS	This revised manuscript addresses the issue of ability of children of a wide age range to swallow and with the revisions made by the authors in light of the comments of previous reviews have

	addressed the issues raised and have provided valuable insights into this under researched area.

REVIEWER	Toine Egberts University Medical Center Utrecht, Utrecht, the Netherlands & Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht, the Netherlands
REVIEW RETURNED	12-May-2020

GENERAL COMMENTS	General remarks: the authors are still not consistent in outcomes, and the authors let me struggle with it. They mention thought the paper (see also title) 4 outcomes: swallowabiility, acceptability, taste, amount of water. In addition, they use for some outcomes multiple assessments (e.g. observation , questioning). I wonder whether a solution would be to define acceptability as the main outcome which is then studied from three angles: swallowability, taste and amount of water and an overall impression of that. Some of the remarks below might be reconsidered if the author would follow my suggestion. I think that the paper benefits from a clear description in the methods: which outcome Is assessed by which measurement(s). - such a clear description could the be used to present the results. In presenting the results on the outcomes I would prefer an ordering per outcome instead of per tablet size. A stable that summarizes the findings for the three tablet sizes would really be helpful. Abstract: present the major findings for all outcomes (swallowability, acceptability, taste , amount of water). In the current abstract only the swallow ability is presented. Feasibility is another aim of the study and assessed by recruitment rates: state the findings Strength: first bullet: only one (acceptability) of the four outcomes is presented Methods swallowability assessment should be understood from reading this manuscript and it should not be necessary to go to reference 5. So: briefly state the method of assessment.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1's comments	Response
This revised manuscript addresses the issue of ability of children of a wide age range to swallow and with the revisions made by the authors in light of the comments of previous reviews have addressed the issues raised and have provided valuable insights into this under researched area.	No further changes needed.

Reviewer 2's comments	**Response**
General remarks: The authors are still not consistent in outcomes, and the authors let me struggle with it. They mention throughout the paper (see also title) 4 outcomes: swallowability, acceptability, taste, amount of water. In addition, they use for some outcomes multiple assessments (e.g. observation, questioning). I wonder whether a solution would be to define acceptability as the main outcome which is then studied from three angles: swallowability, taste and amount of water and an overall impression of that. Some of the remarks below might be reconsidered if the author would follow my suggestion. I think that the paper benefits from a clear description in the methods: which outcome Is assessed by which measurement(s) - such a clear description could then be used to present the results. In presenting the results on the outcomes I would prefer an ordering per outcome instead of per tablet size. A table that summarizes the findings for the three tablet sizes would really be helpful.	Thank you for your suggestion to define acceptability as the main outcome we have updated the title and paper throughout to include main outcome as acceptability. Abstract, methods and results sections have been updated to focus on outcomes as suggested. A new table has been added to summarise overall acceptability (Table 3 - Summary of acceptability results by tablet size).
Abstract: Present the major findings for all outcomes (swallowability, acceptability, taste, amount of water). In the current abstract only the swallowability is presented. Feasibility is another aim of the study and assessed by recruitment rates: state the findings	Updated as requested.
Strength: first bullet: only one (acceptability) of the four outcomes is presented	Updated as requested.
Methods: Swallowability assessment should be understood from reading this manuscript and it should not be necessary to go to reference 5. So: briefly state the method of assessment.	The method of assessment has been updated as requested.

VERSION 3 – REVIEW

REVIEWER	Toine Egberts University medical center Utrecht & Utrecht Institute for Pharmaceutical Sciences, the Netherlands
REVIEW RETURNED	27-Jun-2020

GENERAL COMMENTS	I think the authors did a good job in addressing point raised on previous versions.