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)	Probiotics and the development of very-low-birth-weight infants: Follow up study of a randomized trial
AUTHORS	Totsu, Satsuki; Terahara, Masaki; Kusuda, Satoshi

VERSION 1 - REVIEW

REVIEWER	Rachel Hilliam Institution and Country The Open University UK Competing interests None
REVIEW RETURNED	29-Jan-2018

GENERAL COMMENTS	This is a well written paper with the statistics clearly explained. Whilst I understand that this paper is essentially a follow up and therefore the lack of power calculation has no doubt already been addressed elsewhere, this is still unfortunate. What is also of concern is the use of cluster randomisation which was no doubt carried out for administrative purposes, rather than the more robust method of randomising the actual patients within each facility to one of two treatments, ie within cluster randomisation. It would be helpful to have some explanation as to why the randomisation was not carried out in this way, together with some reassurance that similar patients attend all 19 facilities in terms of demographics. This should include the patients who were not measured due to incomplete data at 18 month follow up. It would also be helpful to know how the numbers of patients were distributed across all 19 units with the demographic information so that concerns regarding selection bias due to the facilities could be addressed. My only other concern is that some of the subgroup analyses are carried out on relatively small numbers. Whilst some of the results are significant this could be due to multiple comparisons, however the authors give clear clinical reasons as to why these are significant. It would however be worth noting that the numbers are relatively small. These are small additions to what is a well written paper from a statistical point of view.

REVIEWER	Kei Lui Institution and Country University of New South Wales, Sydney, Australia Competing interests Nil
REVIEW RETURNED	05-Feb-2018

GENERAL COMMENTS	Totsu et al reported the developmental outcome at 18 months corrected age of a clustered randomised control trial of Bifidobacterium bifidum in <1500 g infants in 19 NICU in Japan. The original trial was powered to examine the impact on enteral feeding and thus the sample size of this outcome study may be limited. Based on ordered logistic regression, the correlation analysis showed a significant difference in comparing the distribution of impairment levels that the beneficial effects of Bifidobacterium were shown. Of the 153 OLB6378 and 130 placebo infants, 102 (67%) and 105 (80%) infants were medically evaluated and developmental levels were categorised for 89 and 79 infants respectively. It would be of interest to know how representative the assessed infants were, and if there were differences in the clinical characteristics between those were assessed and those who were not. This could be included as a supplementary table. Distribution of developmental levels were inferred and categorised for 89 (58% of 153) OLB6378 and 79 (60% of 130) placebo infants. It appears that, 24 (27%) of the OLB6378 infants had MD18 less than 85 and this compared favourably to 32 (40%) of the 79 placebo infants. The authors may wish to include this in the results comparison and analysis, as well as the ordered regression analysis. More details could be included for the potentially confounding factor of IVH. For example, 10 and 23 of the OLB6378 and placebo infants had IVH (presumably all grades of IVH). It would be important to see how many were of major IVH (Grade III or IV) as comparison, which would be of higher risk for developmental impairment. The results were indeed interesting and hypothesis generating. However, there is probably limited role for extended subgroup comparisons and analyses as the assessment rates are not high to allow detailed analysis among the study subgroups (unless there were balanced characteristics between the infants assessed or not). Nonetheless, it showed the OLB6378 infants trended to have better developmental outcome levels. Therefore, Figure 2 may be included as a supplementary e-material and discussions on subgroups may be trimmed in the Discussions. Overall, this study has the potential of being a valuable contribution to literature and clearly larger sample size and higher assessment rates would be of great benefit. Meta-analysis of follow up outcomes of previous trials would be clearly needed. This study is a very good start in stimulating this process. Minor comments Abstract: The 1.5 years should be replaced by 18 months consistent with the DM18 and the rest of the manuscript. The word “stratified” should probably be replaced by “categorised”. The limitation of sample size and low assessment rates could be included. In the conclusion, I recommend to change to “Though limited by assessment rates, result suggests that OLB6378 MAY HAVE a beneficial effect on the psychological development in VLBW infants.

	Table 2: Please clarify "The need of O2" – this probably mean the need of oxygen post discharge. Is this at 18 months or include all discharged for home oxygen?

VERSION 1 – AUTHOR RESPONSE

Response for Reviewer 1

1. p4 line 18: "Study design and participants" of METHODS,
We added the explanation why the randomization was not carried out: "It was speculated that probiotics could be easily spread among infants admitted in the same NICU according to our previous study (6). Therefore, in order to completely avoid infant-to-infant dissemination of OLB6378 within the same NICU, the study was conducted as a cluster-randomized trial.

2. p8 line 19: "Study participants" of RESULTS,
We added supplementary table 1 that shows the numbers of patients were distributed across all 19 units.

3. p11 line 15 and p12 line 2 of "DISCUSSION"
We trimmed the discussion of subgroup according to comments of reviewer 2,

4. p12 line 15: "DISCUSSION"
We added that this study has a limitation of cluster-randomized clinical trial. Because it is difficult to enroll similar patients attend all 19 facilities.

Response for Reviewer 2

1. p2 line 3: "1.5 years" was replaced by "18 months".

2. p2 line 11: "stratified" was replaced by "categorised".

3. p2 line 21: "Conclusion" of ABSTRACT,
Conclusion was changed to "Though limited by assessment rates, result suggests that OLB6378 may have a beneficial effect on the psychological development in VLBW infants.

4. p4 line 14: "1.5 years" was replaced by "18 months".

5. p9 line 2: "Study participants" of RESULT,
We added a comparison if there were differences in the clinical characteristics among 4 groups (assessed or not, B-group or P-group). We also added supplementary table2 to show this comparison.

6. p11 line 15: "DISCUSSION"
To trim the discussion of subgroup, we deleted the discussion of analysis did not show the difference.

7. p12 line 2: "DISCUSSION"
To trim the discussion of subgroup, we deleted the discussion related with gender. And we only introduced the similarity between this study and the report of Partty.
8. p19 Table 1
We added the data of IVH (Grade III or IV)

We also added the data of "Age at enteral feeding exceeding 100 mL/kg/day" of infants who achieved it by 21 days of age.

9. p20 Table 2

We added the data of infants who DQ18 score <85 or developmental test was unfeasible.
We also added the explanation of “Use of O2”; use of oxygen post discharge (This include all discharged for home oxygen)

10. @Supplemental Figure 1

The figure of subgroup was changed to supplementary figure1.

11. @Meta-analysis of follow up outcomes,

There is only one previous study reported by Partty. As the number of trial is too small, we would like to avoid meta-analysis although it would be clearly needed.