Author's response to reviews

Title: A multi-centre randomised placebo-controlled trial for the treatment of non-complicated acute watery diarrhoea using an oral preparation of Lactobacillus acidophilus in Vietnamese children.

Authors:

Marion-Eliëtte Kolader (mkolader@oucru.org)
Ha Vinh (vinhh@oucru.org)
Pham Thi Ngoc Tuyet (tuyetpham57@yahoo.com)
Corinne Thompson (cthompson@oucru.org)
Marcel Wolbers (mwolbers@oucru.org)
Laura Merson (lmerson@oucru.org)
James I Campbell (jcampbell@oucru.org)
Tran Thi Ngoc Dung (dungtttn@oucru.org)
Ha Manh Tuan (manhtuanzu@yahoo.com)
Nguyen Van Vinh Chau (chaunvv@oucru.org)
Jeremy Farrar (jfarrar@oucru.org)
H. Rogier van Doorn (rvandoorn@oucru.org)
Stephen Baker (sbaker@oucru.org)

Version: 2 Date: 5 November 2012

Author's response to reviews: see over
Dear Editor,

Thank you for reviewing the manuscript for the study protocol entitled "A multi-centre randomised placebo-controlled trial for the treatment of non-complicated acute watery diarrhoea using an oral preparation of *Lactobacillus acidophilus* in Vietnamese children" by M. Kolader *et al.*, for potential publication in Trials. Below are the answers to comments made by the handling editor and the reviewer, point by point.

Handling editor comments:

i. Will children who have vomiting at presentation, or have already received an anti-emetic or anti-diarrhoeal agent before entry be excluded, since these events have been considered as treatment failure.

   Answer i.: Children who present with vomiting will not be excluded from entry into the study, but children who have received anti-emetic or anti-diarrhoeal medication at presentation will not be considered eligible. This has been adjusted.

ii. Several outcomes and decisions are subjective, as has also been pointed out by the reviewer. These need explanation or modification of protocol.

   Answer ii.: see answers to the reviewer’s comments below and in the manuscript. The protocol has also been adjusted accordingly.

iii. One of the secondary outcomes is defined as “the total duration of acute watery diarrhoea (including the pre-enrolment duration), that is, the time from the onset of acute watery diarrhoea to the start of the first 24 hour diarrhoea free-period as assessed by the parents/guardians”. This is equal to “time from onset of illness to randomization” plus “time from the first dose of study medication to the start of the first 24 hour diarrhoea free-period as assessed by the parents/guardians” (the primary outcome). Since the time from onset of illness to randomization is likely to be similar in two groups (due to randomization), this secondary outcome has little relevance beyond the primary outcome.

   Answer iii.: Thank you for pointing this out. We agree that there should not be a difference in average time from onset of symptoms to enrolment due to randomization. This endpoint has therefore been deleted from the manuscript and protocol.

iv. The data from authors’ participating hospitals showed “a median hospitalization duration of 5 (interquartile range 3-6) days (mean and standard deviation [SD] of log10-duration is 0.60 and 0.27) in our target population”. Further, they indicate that log-duration showed a normal distribution. This would suggest that 95% of children had log10-duration between 0.06 and 1.14 or duration of illness of 1-14 days. However, elsewhere, the authors state that “children who participated in our previous cross-sectional study in three hospitals in HCMC were discharged after a minimum of at least three days”. These statements are not consistent with each other.

   Answer iv.: Thank you for pointing out this inconsistency. The sentence: “children who participated in our previous cross-sectional study in three hospitals in HCMC were discharged after a minimum of at least three days” has been altered in the protocol and manuscript to: “children who participated in our previous cross-sectional study in three hospitals in HCMC were discharged after a median of five days (range: 1 – 22 days)”.

v. The details of method or software used for sample size calculation should be included.

   Answer v.: Sample size calculation was done using the statistical software programme R v2.15.1. This has been changed.
vi. Analysis is proposed using "log-normal accelerated failure time regression model? A short description of this method or reference to a paper on this method would be useful."

Answer vi.: A reference (27) and a description of the proposed analyses has been added to the protocol and manuscript.

Rebuttal to reviewer SHINJINI BHATNAGAR:

Major comments

The major limitation of this study is that the hypothesis is not clearly stated and the definitions of primary and secondary end points are not objectively defined.

– The hypothesis has been restated.

1. Why is the determination of the primary end point of the study “start of the first 24 hour diarrhoea free period” dependent on the parents/guardians (‘as assessed by the parents/guardians) and not the research staff? Asking parents/guardians to judge the primary endpoint will introduce subjectivity in the measurement of the outcome. The research staff can be trained to remove inter and intra observer variability which may not be possible with the parents/guardians

Answer 1): The primary endpoint of the first 24-hour period as defined by the parents/guardians, was chosen to determine a more accurate timing of the diarrhoeal episodes as the nurses on duty check on patients at the beginning of their shift and when necessary, but not for every diarrhoeal episode.

The primary endpoint has been adapted to the following: “The primary endpoint is the time from the first dose of study medication to the start of the first 24-hour period without diarrhoea free period, as assessed by the nurse on duty.”

Parents will be given an hourly checklist in which to record diarrheal and vomiting episodes during a 24 hour period. This is then collected by the nurses on duty during the first of their normal rounds.

The secondary endpoint has been adapted to the following: “The time from the first dose of study medication to the start of first 24-hour diarrhoea free period as recorded by parents/guardians in a hourly checklist, collected by the nurses on duty every 12 hours.”

2. The definitions of some of the outcomes are very subjective:
   • “Discontinuation of the study medication will depend on the discretion of the study physician”
   • “Physicians will determine day and moment of discharge at their discretion”

These definitions should be clearly stated and not depend on the discretion of the study physician.

Answer 2): “Discontinuation of the study medication will depend on the discretion of the study physician” and “Physicians will determine day and moment of discharge at their discretion” have been deleted and the paragraph has been altered.

3. Details on randomization process are not adequately provided.

Answer 3): The paragraph on randomization has been changed.

Minor comments:

The authors need to explain why subjects screened for the study are between 9-60 months?

Answer to minor comments: the reason for screening patients between the ages of 9 months and 60 months has been added to the text in the protocol and manuscript to: “This age group was selected as healthy children (< 9 months of age) have less solid stools than those in an older age category, making the cessation of diarrheal symptoms more difficult to assess.”

The manuscript was also revised for language corrections. A revised manuscript has been enclosed in which the above changes have been highlighted. We hope that the answers are such that you will make a positive decision for publication in Trials.

Yours sincerely,

Dr. Marion Kolader, MD
On behalf of Dr. Stephen Baker, BSc PhD