PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Lactobacillus reuteri DSM 17938 for managing infant colic - protocol for an individual participant data meta-analysis
AUTHORS	Sung, Valerie; Cabana, Michael; D'Amico, Frank; Deshpande, Girish; Dupont, Christophe; Indrio, Flavia; Mentula, Silja; Partty, Anna; Savino, Francesco; SZAJEWSKA, Hania; Tancredi, Daniel

VERSION 1 - REVIEW

REVIEWER	William E. Bennett, Jr., M.D. Indiana University School of Medicine, USA
REVIEW RETURNED	10-Sep-2014

GENERAL COMMENTS	Overall: This is a very well designed IPDMA. The methods used are all completely appropriate and well thought out. This protocol has a high chance of creating results with a high impact on clinical care. My only hesitation is some of the language indicates an a priori assumption that probiotics are effective for colic, something that a meta-analysis (and especially an IPD meta-analysis) should not make. The authors clearly have a great deal of experience putting together well-designed clinical research, and the resulting IPDMA has a high chance of success. Introduction Page 5, Line 14-15 - Families rejecting supportive care for a benign, self-limited problem is not sufficient reason to justify research into probiotics as a cure for colic. Health care professionals prescribing medicine inappropriately is not a reason to justify research into probiotics as a cure for colic. Based on these statements, there is not "a need to find a safe and effective treatment option for infant colic." We have a safe and effective treatment option already: reassurance and family support. The first paragraph seems as if probiotics are being presumed to be effective a priori. There are plenty of reasons to explore the cause for colic and potential treatments, but parents and physicians rejecting supportive care is not a particularly compelling one. Page 5, Paragraph 3 - The reasons enumerated here are the reasons to do the IPDMA, and are stated perfectly. Indeed, this is the reason to do almost any IPDMA. I think making this argument from the start is far more important than making the argument put forth in Paragraph 1. Page 6, Line 23 - I'm not sure that the references supplied back up the point made by the authors. "Individual probiotic strains may be effective for colic via different potential mechanisms." This is pure speculation and I would avoid it, since it has not been conclusively proven that probiotics are effective for colic, or that dysbiosis

	underlies the pathogenesis of colic to begin with. Page 6, Line 32 - The aims are well described. I agree that restricting to L. reuteri is appropriate and increases the chance for success. Methods Page 7, Line 8 - Very wise to use the Cochrane guidelines for IPDMAs. Page 7, Line 33 - In the main outcomes, please justify the use of 21 days as a primary outcome and 7, 14, and 28 as secondary outcomes. Many trials used 28 days as a primary outcome. Is it because of the structure in existing trials' outcomes? Seems unusual. Page 7, Line 33 - Also in the main outcomes, please specify what type of main outcome data you will accept. Is it only enumerated outcomes (# of crying hours), or will you accept binary responses from parents without quantifying (e.g. "Did your baby have a 50% reduction in crying.") Page 7, Line 41 - Why not look for family functioning / QOL / etc? Since this is the reason given in the first paragraph for why research into probiotic effectiveness is so important? Why no patient centered outcomes? You might not find them in many publications, but they should certainly be looked for. Page 8, Paragraph 3 - The authors suggest that having sufficient power is enough, and that if they meet their power calculations, then we can trust the outcomes. This is not the case for an IPDMA. If all trials aren't adequately represented, the results can be biased considerably, even if power is sufficient. Please enumerate in detail how you will assure that sufficient representation of all trials will occur. Ethics and Dissemination Page 10, Line 27 - Also include the risk that you don't get adequate representation of all trial participants and data is skewed by which trials you were able to get data on. My hope is this won't be a problem, but worth addressing proactively!

REVIEWER	Carolina de Weerth Developmental Psychology Behavioural Science Institute Radboud University The Netherlands
REVIEW RETURNED	15-Sep-2014

GENERAL COMMENTS	I am not familiar with IPDMA, and although the technique is clearly explained and seems straightforward, perhaps a statistician should check it. General I am not familiar with the IPDMA, but am very enthusiastic about the authors' description of the analyses. IPDMA appears to have

	important advantages that will permit the authors to investigate very relevant issues on the topic of the effectiveness of the probiotic Lactobacillus reuteri DSM17938 for the treatment of colic. A study of this type is very much needed in the field. The involvement of two independent statisticians in the study is a strong methodological point. Specific points Under Strengths and limitations of the study: I think that a limitation that should be mentioned is that the authors will include studies using very different methods to determine whether an infant has colic, namely diaries, questionnaires and parental interviews. This is most probably unavoidable as it is common practice in clinical settings to use different methods of determining whether an infant has colic, but it does constitute a limitation, as studies may sometimes be including infants that do not actually suffer from colic in their RCT's. The proportion of infants that actually do not have colic may therefore vary considerably between studies, depending on how objective their methods for determining colic are. Page 6 of 14, line 17 on: "The pooling of data into an IPDMA for analysis will ultimately provide more definitive answers as to whether the probiotic Lactobacillus reuteri DSM17938 is effective for infant colic, and determine which subgroups of infants would benefit from which particular probiotic strain." Shouldn't it say 'this' instead of 'which'? The authors will only be looking at potential effects of the L. reuteri DSM17938, so they won't be able to conclude anything about other probiotic strains. Page 9 of 14, line 22 on: "Confounders identified a priori will include 1) family history of atopy, 2) delivery type (vaginal versus caesarian), and 3)enrolment age." Shouldn't the use of antibiotics also be included as a confounder?

VERSION 1 – AUTHOR RESPONSE

Reviewer Name William E. Bennett, Jr., M.D.
Institution and Country Indiana University School of Medicine, USA
Please state any competing interests or state 'None declared': None declared.

Overall: This is a very well designed IPDMA. The methods used are all completely appropriate and well thought out. This protocol has a high chance of creating results with a high impact on clinical care. My only hesitation is some of the language indicates an a priori assumption that probiotics are effective for colic, something that a meta-analysis (and especially an IPD meta-analysis) should not make. The authors clearly have a great deal of experience putting together well-designed clinical research, and the resulting IPDMA has a high chance of success.

Introduction

Page 5, Line 14-15 - Families rejecting supportive care for a benign, self-limited problem is not sufficient reason to justify research into probiotics as a cure for colic. Health care professionals prescribing medicine inappropriately is not a reason to justify research into probiotics as a cure for colic. Based on these statements, there is not "a need to find a safe and effective treatment option for infant colic." We have a safe and effective treatment option already: reassurance and family support. The first paragraph seems as if probiotics are being presumed to be effective a priori. There are

plenty of reasons to explore the cause for colic and potential treatments, but parents and physicians rejecting supportive care is not a particularly compelling one.

*Thank you, the introductory text has been amended to reflect your comments.

Page 5, Paragraph 3 - The reasons enumerated here are the reasons to do the IPDMA, and are stated perfectly. Indeed, this is the reason to do almost any IPDMA. I think making this argument from the start is far more important than making the argument put forth in Paragraph 1.

*Thank you, the introductory text has been amended to reflect your comments.

Page 6, Line 23 - I'm not sure that the references supplied back up the point made by the authors. "Individual probiotic strains may be effective for colic via different potential mechanisms." This is pure speculation and I would avoid it, since it has not been conclusively proven that probiotics are effective for colic, or that dysbiosis underlies the pathogenesis of colic to begin with.

*Thank you, the sentence has been altered and only the most relevant reference included.

Page 6, Line 32 - The aims are well described. I agree that restricting to L. reuteri is appropriate and increases the chance for success.

Methods

Page 7, Line 8 - Very wise to use the Cochrane guidelines for IPDMAs.

Page 7, Line 33 - In the main outcomes, please justify the use of 21 days as a primary outcome and 7, 14, and 28 as secondary outcomes. Many trials used 28 days as a primary outcome. Is it because of the structure in existing trials' outcomes? Seems unusual.

*21 days was the most commonly studied time point and the primary outcome time point in 2 out of the 3 trials involving L reuteri DSM17938.

Page 7, Line 33 - Also in the main outcomes, please specify what type of main outcome data you will accept. Is it only enumerated outcomes (# of crying hours), or will you accept binary responses from parents without quantifying (e.g. "Did your baby have a 50% reduction in crying.")

*We have added “parental report of treatment success” as an additional secondary outcome.

Page 7, Line 41 - Why not look for family functioning / QOL / etc? Since this is the reason given in the first paragraph for why research into probiotic effectiveness is so important? Why no patient centered outcomes? You might not find them in many publications, but they should certainly be looked for.

*We have added maternal depression, quality of life, and family functioning as additional secondary outcomes. As the reviewer suggests, these data are not available from every study. We have also a statement to the protocol that we will analyse all available data for secondary outcomes.

Page 8, Paragraph 3 - The authors suggest that having sufficient power is enough, and that if they meet their power calculations, then we can trust the outcomes. This is not the case for an IPDMA. If all trials aren't adequately represented, the results can be biased considerably, even if power is

sufficient. Please enumerate in detail how you will assure that sufficient representation of all trials will occur.

*We have added the following sentence to the end of the paragraph on eligibility criteria: “All authors of eligible trials have been contacted and invited to participate in this IPDMA. As more trials satisfying eligibility criteria become published, the relevant authors will be approached and invited to participate, as long as their trials are published within the timeframe of conducting this IPDMA.”

Ethics and Dissemination

Page 10, Line 27 - Also include the risk that you don't get adequate representation of all trial participants and data is skewed by which trials you were able to get data on. My hope is this won't be a problem, but worth addressing proactively!

*The following sentence has been added: “There is also a risk of inadequate representation of all trial participants due to authors who do not consent to their data being pooled into the IPDMA.”

Reviewer Name Carolina de Weerth
Institution and Country Developmental Psychology
Behavioural Science Institute
Radboud University
The Netherlands
Please state any competing interests or state ‘None declared’: None declared.

General
I am not familiar with the IPDMA, but am very enthusiastic about the authors’ description of the analyses. IPDMA appears to have important advantages that will permit the authors to investigate very relevant issues on the topic of the effectiveness of the probiotic Lactobacillus reuteri DSM17938 for the treatment of colic. A study of this type is very much needed in the field. The involvement of two independent statisticians in the study is a strong methodological point.

Specific points
Under Strengths and limitations of the study: I think that a limitation that should be mentioned is that the authors will include studies using very different methods to determine whether an infant has colic, namely diaries, questionnaires and parental interviews. This is most probably unavoidable as it is common practice in clinical settings to use different methods of determining whether an infant has colic, but it does constitute a limitation, as studies may sometimes be including infants that do not actually suffer from colic in their RCT’s. The proportion of infants that actually do not have colic may therefore vary considerably between studies, depending on how objective their methods for determining colic are.

*The following has been added as a limitation:
“The study is also limited by inclusion of studies with differing methods of defining infant colic and measuring outcomes.”

Page 6 of 14, line 17 on: “The pooling of data into an IPDMA for analysis will ultimately provide more definitive answers as to whether the probiotic Lactobacillus reuteri DSM17938 is effective for infant colic, and determine which subgroups of infants would benefit from which particular probiotic strain.” Shouldn’t it say ‘this’ instead of ‘which’? The authors will only be looking at potential effects of the L. reuteri DSM17938, so they won’t be able to conclude anything about other probiotic strains.

*Thank you, the text has been altered.

Page 9 of 14, line 22 on: “Confounders identified a priori will include 1) family history of atopy, 2) delivery type (vaginal versus caesarian), and 3)enrolment age.” Shouldn’t the use of antibiotics also be included as a confounder?

*Thank you, antibiotic use has been added as a potential confounder.