

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

### ARTICLE DETAILS

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| <b>TITLE (PROVISIONAL)</b> | EFFECTIVENESS OF OSTEOPATHIC MANIPULATIVE TREATMENT IN NEONATAL INTENSIVE CARE UNITS: PROTOCOL FOR A MULTICENTRE RANDOMIZED CLINICAL TRIAL            |
| <b>AUTHORS</b>             | Cerritelli, Francesco; Pizzolorusso, Gianfranco; Renzetti, Cinzia; D'Incecco, Carmine; Fusilli, Paola; Perri, Paolo; Tubaldi, Lucia; Barlafante, Gina |

### VERSION 1 - REVIEW

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| <b>REVIEWER</b>        | Maria Rosaria Cesarone, Pediatrician, Angiologist<br>Dip. Scienze Biomediche Università G D'Annunzio, Chieti |
| <b>REVIEW RETURNED</b> | 29-Oct-2012  |

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| <b>GENERAL COMMENTS</b> | The study is well performed and described.<br>It open the way for further studies on preterm infants and the possibility of new treatments to be associated with the classical.<br>Very important is the aim to reduce the time of hospitalitation and complications, with consequent reduction of social costs. |
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| <b>REVIEWER</b>        | Dr Patricia Giuliani MD<br>Senior researcher<br>Department of Experimental and Clinical Sciences<br>Section of Pharmacology<br>University of Chieti-Pescara, Italy<br><br>I have no conflicts of interests in this paper, I am a researcher at the University of Chieti-Pescara and I have a teaching contract with the Accademia Italiana Osteopatia tradizionale. |
| <b>REVIEW RETURNED</b> | 09-Nov-2012   |

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| <b>THE STUDY</b>        | Are the abstract/summary/key messages/limitations accurate?<br>- In the abstract the analysis section is lacking. In my opinion It is useful for the reader to include it.<br><br>Is the standard of written English acceptable for publication?<br>- Page 5 lines 14-16: the sentence " The average cost per infant ..... " result to be not clear and should be reworked to avoid confusion.<br><br>- Authors should be careful in the use of abbreviations or acronyms throughout the manuscript. Only the first time they use them within the paper or in the abstract, they should place it in parentheses immediately following the complete term. |
| <b>GENERAL COMMENTS</b> | Authors should review and correct the reference number 11 since from July 2011 the legal association of WOHO is discontinued.  |

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|  | Regarding the “methods and analysis” section (the population paragraph, page 7, lines 21-22), the authors should clearly define the two groups ie “patient under usual medical care plus OMT and patients that receive only usual medical care”. |
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| <b>REVIEWER</b>        | Melicien Tettambel, DO,FAAO,FACCOG<br>Professor and Chair Osteopathic Principles and Practice<br>Pacific Northwest University of Health Sciences-College of<br>Osteopathic Medicine<br>Yakima, WA. USA<br><br>No competing interests |
| <b>REVIEW RETURNED</b> | 24-Nov-2012  |

- The reviewer completed the checklist but made no further comments.

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| <b>REVIEWER</b>        | Florian Schwerla MSc, D.O.<br>German Academy of Osteopathy<br>Research Commission<br><br>no conflict of interest |
| <b>REVIEW RETURNED</b> | 02-Dec-2012  |

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| <b>GENERAL COMMENTS</b> | Title: In the title the authors used the word „efficacy“, in abstract and text „effectiveness“. Both are very different terms. Because the study is a pragmatic study, the word effectiveness is right. Please change the word in your title.<br>Introduction: It would be helpful to have some information about how many days the LOS normally lasts (depending on the time of birth) and what the costs/day are.<br>Methods: The authors mentioned that the osteopaths have to have 5 years of practice. Can you explain that a little more in detail: Are they working in a hospital or in a private practice, what education did they have? Further I could not find how long the osteopathic treatment lasts.<br>Aim of the study: The authors write: “primary endpoint”. To use the term “primary (or secondary) outcome parameter” would be more clear for me.<br>Statistics: The authors mentioned the univariate statistical test and linear regression model. For an RCT like this perhaps the t-test for the comparison of the two groups is more useful to identify a causal impact of OMT on LOS. |
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| <b>REVIEWER</b>        | Natalie M. Hayes, D.O.<br>Wake Forest Baptist Health<br>Department of Pediatrics<br>Division of Pulmonology<br>Winston-Salem, NC USA<br>position: Pediatric Pulmonologist |
| <b>REVIEW RETURNED</b> | 19-Dec-2012   |

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| <b>THE STUDY</b> | <p>In the abstract and methods, the objective states the aim of the study is to examine the association between OMT and LOS, whereas in the introduction the aim discusses clinical observations. A more detailed explanation of the study's aim in the introduction is needed, and should be consistent throughout the manuscript. The population states all preterm infants, then later excludes any infant less than 29 weeks, so an inclusion criteria would be gestational age between 29-37 weeks.</p> <p>A sham group is not included, which is needed. It sounds as if all subjects will have an osteopathic structural examination, which can effect the outcome (no group is truly getting just "usual care"). "Osteopath" needs to be defined, and re-named. What is the training? In the US, a doctor of osteopathy (D.O.) has 4 years of osteopathic medical school training, and that may not be the case in all countries. Is the person doing structural examinations and OMT an osteopathic physician, a physiotherapist, etc?</p> <p>There needs to be discussion regarding the duration of each OMT session and which specific techniques will be used (if different among subjects, this could affect outcomes). More discussion is needed for non-osteopathic physicians regarding osteopathic techniques, such as rib-raising, doming the diaphragm, soft tissue techniques, etc. (whatever techniques are used), and how they help with certain somatic dysfunctions.</p> <p>If able, update references with a prospective study regarding safety in pediatric OMT, as reference 18 is a retrospective study. Statistical analysis and randomization process is deferred for biostatistician review.</p> |
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### VERSION 1 – AUTHOR RESPONSE

Answers to reviewer number 2: Maria Rosaria Cesarone, Pediatrician, Angiologist  
Dip. Scienze Biomediche Università G D'Annunzio, Chieti

Comment [1]: The study is well performed and described.

It open the way for further studies on preterm infants and the possibility of new treatments to be associated with the classical. Very important is the aim to reduce the time of hospitalitation and complications, with consequent reduction of social costs.

A: OK

Answers to reviewer number 3: Dr Patricia Giuliani MD - Senior researcher  
Department of Experimental and Clinical Sciences - Section of Pharmacology  
University of Chieti-Pescara, Italy

Comment [1]: In the abstract the analysis section is lacking. In my opinion It is useful for the reader to include it.

A: OK. The following sentence has been added "Statistical analyses will take into account the intention-to-treat method. Missing data will be handled using last observation carried forward imputation technique."

Comment [2]: Page 5 lines 14-16: the sentence " The average cost per infant ..... " result to be not clear and should be reworked to avoid confusion.

A: OK. The sentence was changed as follows: "The highest average cost per infant is for preterm newborns with gestational age (GA) between 24-31 weeks, followed by those between 32-36 weeks, as opposed to the general population"

Comment [3]: Authors should be careful in the use of abbreviations or acronyms throughout the manuscript. Only the first time they use them within the paper or in the abstract, they should place it in parentheses immediately following the complete term.

A: OK. Done

Comment [4]: Authors should review and correct the reference number 11 since from July 2011 the legal association of WHO is discontinued.

A: OK. Reference updated

Comment [5]: Regarding the "methods and analysis" section (the population paragraph, page 7, lines 21-22), the authors should clearly define the two groups ie "patient under usual medical care plus OMT and patients that receive only usual medical care".

A: OK. The sentence has been changed: "Preterm infants entering the trial will receive either routine medical care plus osteopathic evaluation and treatment or routine medical care plus osteopathic evaluation only"

Answers to reviewer number 4: Melicien Tettambel, DO,FAAO,FACCOG - Professor and Chair Osteopathic Principles and Practice - Pacific Northwest University of Health Sciences-College of Osteopathic Medicine - Yakima, WA. USA

(There are no comments.)

A: OK

Answers to reviewer number 5: Florian Schwerla MSc, D.O. - German Academy of Osteopathy - Research Commission

Comment [1]: Title: In the title the authors used the word „efficacy“, in abstract and text „effectiveness“. Both are very different terms. Because the study is a pragmatic study, the word effectiveness is right. Please change the word in your title.

A: OK. Done

Comment [2]: Introduction: It would be helpful to have some information about how many days the LOS normally lasts (depending on the time of birth) and what the costs/day are.

A: OK. The following two sentences were added: "In Italy, the cost per infant per day ranged between €200 and €500 according to infants health conditions" and "The italian healthcare institute reported an average LOS per different diagnostic categories ranging from 4 to 34 days"

Comment [3]: Methods: The authors mentioned that the osteopaths have to have 5 years of practice. Can you explain that a little more in detail: Are they working in a hospital or in a private practice, what education did they have? Further I could not find how long the osteopathic treatment lasts.

A: OK. The manuscript has been implemented as follows: "osteopaths with at least 5 years of osteopathic treatments in NICU and specialized neonatal osteopathic education." Moreover, the following sentences have been added: "The whole session will last 30 minutes, 10 minutes for evaluation and 20 minutes for treatment" and "The osteopathic evaluation will last 10 minutes. To maintain blinding of NICU personnel, the following 20 minutes osteopaths will keep their position close to the incubator or bed without touching the infant."

Comment [4]: Aim of the study: The authors write: “primary endpoint”. To use the term “primary (or secondary) outcome parameter” would be more clear for me.

A: OK. The term “endpoint” has been substituted with “outcome”

Comment [5]: Statistics: The authors mentioned the univariate statistical test and linear regression model. For an RCT like this perhaps the t-test for the comparison of the two groups is more useful to identify a causal impact of OMT on LOS.

A: Disagree. The t-test is part of the univariate analysis thus it will be performed. Linear regression analysis will provide more robust results as it looks at the independent effect of independent factors (i.e. OMT) on the dependent variable (LOS).

Answers to reviewer number 6: Natalie M. Hayes, D.O. - Wake Forest Baptist Health - Department of Pediatrics

Division of Pulmonology - Winston-Salem, NC USA - position: Pediatric Pulmonologist

Comment [1]: In the abstract and methods, the objective states the aim of the study is to examine the association between OMT and LOS, whereas in the introduction the aim discusses clinical observations. A more detailed explanation of the study's aim in the introduction is needed, and should be consistent throughout the manuscript.

A: OK. The following statement has been inserted: “Aim of this multicentre randomized controlled trial is to examine the association between OMT and LOS in a larger population.”

Comment [2]: The population states all preterm infants, then later excludes any infant less than 29 weeks, so an inclusion criteria would be gestational age between 29-37 weeks.

A: OK. The name of the paragraph has been changed in “Exclusion criteria”

Comment [3]: A sham group is not included, which is needed.

A: Agree, but due to budgetary and logistic constraints the trial has been designed without a sham group

Comment [4]: It sounds as if all subjects will have an osteopathic structural examination, which can affect the outcome (no group is truly getting just "usual care").

A: Agree, but the trial has been designed to avoid potential confutations from the NICU personnel thus all preterms will be at least touched.

Comment [4]: "Osteopath" needs to be defined, and re-named. What is the training? In the US, a doctor of osteopathy (D.O.) has 4 years of osteopathic medical school training, and that may not be the case in all countries. Is the person doing structural examinations and OMT an osteopathic physician, a physiotherapist, etc?

A: Disagree. D.O. Eur are fully license practitioners with a Diploma in Osteopathy (DO). The term osteopath is also used allover Europe and it refers to those who attended a certified osteopathic school (5 or 6 years) regardless if they have got a previous degree in medicine or physiotherapy.

Comment [5]: There needs to be discussion regarding the duration of each OMT session and which specific techniques will be used (if different among subjects, this could affect outcomes).

A: OK. The duration has been added. The type of techniques used has been specified but no formal treatment protocol has been designed. The “black-box” method has been used. Moreover, the aim of the study is to look at the effectiveness of osteopathic treatment and not at the efficacy of any specific technique.

Comment [6]: More discussion is needed for non-osteopathic physicians regarding osteopathic techniques, such as rib-raising, doming the diaphragm, soft tissue techniques, etc. (whatever techniques are used), and how they help with certain somatic dysfunctions.

A: See comment [5]

Comment [7]: If able, update references with a prospective study regarding safety in pediatric OMT, as reference 18 is a retrospective study.

A: Agree, but no prospective safety study has been carried out yet.

Comment [8]: Statistical analysis and randomization process is deferred for biostatistician review.

A: OK.