PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Manual therapy for unsettled, distressed and excessively crying infants: a systematic review and meta-analyses.
AUTHORS	Carnes, Dawn; Plunkett, Austin; Ellwood, Julie; Miles, Clare

VERSION 1 – REVIEW

REVIEWER	Hilary Abbey The British School of Osteopathy 275 Borough High Street London SE1 1JE UK
REVIEW RETURNED	12-Aug-2017

GENERAL COMMENTS	This clearly written paper presents comprehensive details about paediatric topics that are currently of interest for manual therapists. It outlines rigorous analytic processes and presents comprehensive results, but large tables in the Results section may be overwhelming for some readers and might be presented in a more digestible form. The studies in Table 1 (p.14) are currently arranged in alphabetical order. Key content might be easier to digest if studies were presented according either to the hierarchy of evidence (e.g. RCTs at the top and the qualitative study at the bottom) or in order of appraisal quality (high to low). Table 2 is also large and could be split into two tables; one presenting categories with moderate evidence, and the other for lesser evidence? In some places there seem to be missing commas, and punctuation could make the meaning of some sentences clearer e.g. page 10, line 1 - 'For non RCT studies, the analyses were...'; and page 11, lines 6-7, add commas either side of 'for example'.

REVIEWER	Francesco Cerritelli University of Chieti-Pescara - Italy
REVIEW RETURNED	19-Aug-2017

GENERAL COMMENTS	The author presented a systematic review aiming at synthesising the literature on the effect of manual therapies on unsettled infants. The findings showed a debatable scenario of the effect of manual treatment. Several methodological flaws interfere with the robustness and appropriateness of their results. General comments The research is certainly of interest but according to how it was conducted and planned it seems providing the same conclusions of a previous Cochrane paper (Dobson et al, 2012) without adding much to the current literature. Indeed the authors stated that from 2012 no RCTs were conducted but they carried out the systematic review anyway, thus replicating the Dobson et al 2012's paper. One of the requirements that Cochrane suggests is to analyse the literature first (before carrying out the research) and see if it is worth to conduct a new systematic review. Moreover, the statistics needs to be reviewed as, according to Cochrane guidelines, an high I2 might implies high heterogeneity and therefore it is recommended to avoid pulling the data. Thus an I2 of 65% clearly shows high heterogeneity and therefore no meta-analysis is recommended. Furthermore, the authors are invited to analyse also other type of heterogeneity, i.e. methodological, clinical and statistical, which might change completely the analysis of studies included. The interpretation of RR meta-analysis needs to be reviewed as "those who had manual therapy had 0.12 times the risk of having an adverse events compared to those who did not have manual therapy, i.e. a reduced risk" is a wrong statement. There is a decrease of the risk by 88% Then in the method section, it is not declared if they would use a random or fixed effects as well as other methodological aspects of the meta-analysis that were not taken into consideration. They have included different methodologies from which one cannot claim effectiveness or efficacy nor causality - eg qualitative research - despite that they seem to infer clinical effectiveness from those studies. The strategy for selecting the paper is unusual as 2 teams by 2 people increase significantly the chance of producing bias. Then it is unclear how the arbiter (aka third reviewer in the paper) dealt with paper inclusion discussion. Usually the arbiter is external to the reviewers. Plus, for consistency and transparency, there is the need to state what were the papers discussed. Authors meant to include all the languages but eventually they excluded just one Chinese paper (for language issue) but then in the discussion they argued that several research from China were took into consideration. This needs to be addressed as per consistency and clarity. Minor revisions: some misspelled words and parts of the paper that need revision

REVIEWER	Serge Brand University of Basel, Psychiatric Clinics (UPK)
REVIEW RETURNED	26-Aug-2017

GENERAL COMMENTS	The authors present a systematic review of manual therapies to treat infants' excessive crying behavior and showed that the overall influence of manual therapies is moderate to mixed. The topic is interesting and important. I suggest to expanding the introduction section: First, crying is almost the infants' only means to signaling needs to caregivers. Accordingly, second, excessive crying is considered the upper end of the range of early developmental crying behavior. Third, excessive crying seems to be unrelated to parents' behavior and parents' cultural background (St James-Roberts et al 2006, Pediatrics; Talachian et al 2008 World J Gastroenterol). Fourth, excessive crying is regarded as reflecting individual differences in maturation of the central nervous system (Barr 2002 Arch Pediatr Adol Med). Accordingly, fifth, in most cases, excessive crying is not related to gastrointestinal issues. „Many aetiological factors for unsettled infant behaviour have been explored including digestive, musculoskeletal, breastfeeding and parenting problems [8-22]"; please, be more specific with this statement; clearly indicate which references do refer to which problem. Given the methodological importance of Ref 23, I suggest to describing the content and the result of that publication in more details. The systematic review has been conducted following the standards. Conclusions are rigorously based on the extracted data.

REVIEWER	Nai Ming Lai Taylor's University, Malaysia
REVIEW RETURNED	27-Aug-2017

GENERAL COMMENTS	This is a well-conducted systematic review and meta-analysis that attempted to update a recent Cochrane review on the same topic, with broader inclusion criteria of non-randomised studies aiming to include more parent-reported outcomes and reports of adverse events, although there were not much important new information to add from those non-randomised studies. Nonetheless, this updated review is important as it highlights the existing gaps in literature that assess parent-reported outcomes and parent-infant psychosocial assessments. Overall, the manuscript is well-written and easy to read, although I would have expected more specific details in the way of recommendations for future research, especially non-randomised trials, in particular specific outcomes to be evaluated (including recommended measuring tools such as scales) or scope of related qualitative studies, since these were the types of studies that the authors attempted to incorporate to get a richer perspective on the benefits and perception on manual therapy. Below are some additional minor comments relating to specific parts of the manuscript: Abstract, results: adverse effects should be reported comparatively (manual therapy versus control). At present it is only reported in the group that received manual therapy.

	Main text. Methods, Strength of evidence: What were the specific criteria to judge whether the conclusions were likely or unlikely to be affected by future studies? Results, reduction in crying time: I suggest the authors present the results after limiting studies to parent-blinded studies, as in the recent Cochrane review. Figure 2: I square is 69%, suggesting substantial heterogeneity, which seems to be contributed by a single study Olafsdottir 2001. Was there any exploration done on possible reasons that might have contributed to the heterogeneity in the estimates? Adverse events: the authors included "worsening symptoms" as part of the adverse events which I query. I would have thought worsening symptoms is part of the main outcome that related to the effectiveness (or "ineffectiveness") of the intervention assessed, and not adverse effects (which is usually unexpected). Please consider addressing this.

REVIEWER	Dr Viswas Chhapola Lady Hardinge Medical College, New Delhi, India
REVIEW RETURNED	10-Sep-2017

GENERAL COMMENTS	Authors have attempted to perform a comprehensive literature search and performed the meta-analysis using both RCT and observational studies. There are few points on which the manuscript needs improvement 1. Authors should use PRISMA for abstract guideline to write the abstract. 2. Authors have followed most of steps of conducting a systematic review and meta-analysis. 2. The meta-analysis has studies which are similar to studies by Dobson etal. No new studies were available for inclusion in quantitative meta-analysis. So the conclusions are not expected to be any different either. The more important strength of current met-analysis should be the inclusion of observational studies. Authors have well summarised the observational studies in tables. However, a strong qualitative synthesis of observational studies has not been done. Authors should strengthen the qualitative synthesis of observational studies which they were not able to include in meta-analysis. The conclusions should be drawn on basis of both quantitative and qualitative synthesis. For guidance on conducting qualitative synthesis the authors should consult the publication from National academies press entitled “Finding What Works in Health Care: Standards for Systematic Reviews”.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Hilary Abbey
Institution and Country: The British School of Osteopathy, 275 Borough High Street, London SE1 1JE, UK
Competing Interests: None declared

Comment: This clearly written paper presents comprehensive details about paediatric topics that are currently of interest for manual therapists. It outlines rigorous analytic processes and presents comprehensive results, but large tables in the Results section may be overwhelming for some readers and might be presented in a more digestible form. The studies in Table 1 (p.14) are currently arranged in alphabetical order. Key content might be easier to digest if studies were presented according either to the hierarchy of evidence (e.g. RCTs at the top and the qualitative study at the bottom) or in order of appraisal quality (high to low). Table 2 is also large and could be split into two tables; one presenting categories with moderate evidence, and the other for lesser evidence?
In some places there seem to be missing commas, and punctuation could make the meaning of some sentences clearer e.g. page 10, line 1 - 'For non RCT studies, the analyses were...'; and page 11, lines 6-7, add commas either side of 'for example'.

Response: We have proof read the manuscript and hope that the punctuation issues have been resolved. In addition we have re-ordered Table 1 into types of studies. This new ordering is reflected in the new table 2 for quality appraisal. We have deleted all the data extractions for the low quality studies from Table 3 which has shortened this table and made it easier to read.

Reviewer: 2
Reviewer Name: Francesco Cerritelli
Institution and Country: University of Chieti-Pescara - Italy
Competing Interests: None declared

The author presented a systematic review aiming at synthesising the literature on the effect of manual therapies on unsettled infants. The findings showed a debatable scenario of the effect of manual treatment. Several methodological flaws interfere with the robustness and appropriateness of their results.

General comments
The research is certainly of interest but according to how it was conducted and planned it seems providing the same conclusions of a previous Cochrane paper (Dobson et al, 2012) without adding much to the current literature. Indeed the authors stated that from 2012 no RCTs were conducted but they carried out the systematic review anyway, thus replicating the Dobson et al 2012's paper. One of the requirements that Cochrane suggests is to analyse the literature first (before carrying out the research) and see if it is worth to conduct a new systematic review.

Response: We found two additional RCTs (Nue et al 2014 and Herzhalf-Le Roy 2017) but neither reported outcomes on crying time suitable for addition into a new meta-analysis. In addition we were very clear that this review would include non-RCTs in addition. Please see new text in the discussion as shown in the response to the Editor's comments to illustrate the added value of incorporating the non-RCT studies.

Comment: Moreover, the statistics needs to be reviewed as, according to Cochrane guidelines, an high I2 might implies high heterogeneity and therefore it is recommended to avoid pulling the data. Thus an I2 of 65% clearly shows high heterogeneity and therefore no meta-analysis is recommended. Furthermore, the authors are invited to analyse also other type of heterogeneity, i.e. methodological, clinical and statistical, which might change completely the analysis of studies included.

Response: The I2 statistic informs the reader of the extent of heterogeneity of the studies. We expect heterogeneity with studies of this nature. An I2 of 69% can be classified as moderate (Higgins J, Thompson SG, Deeks J, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414): 557-560.). The Dobson et al Cochrane review also showed a range of I2 statistics from 55% to 75%. We discuss heterogeneity in further detail in the discussion:
'The I2 statistic in our meta-analysis and Dobson et al's (2014) were 69% and 55% respectively, indicating heterogeneity between the studies analysed. This was not unexpected due to the potential variation in treatments (and hence effects), loose diagnostic criteria and power of the samples for the RCTs. Therefore, the results have to be considered with this in mind and used to inform further research for well powered studies, flexible but protocolised treatment and parental blinding.'

Comment: The interpretation of RR meta-analysis needs to be reviewed as "those who had manual therapy had 0.12 times the risk of having an adverse events compared to those who did not have manual therapy, i.e. a reduced risk" is a wrong statement. There is a decrease of the risk by 88%
Then in the method section, it is not declared if they would use a random or fixed effects as well as other methodological aspects of the meta-analysis that were not taken into consideration. They have included different methodologies from which one cannot claim effectiveness or efficacy nor causality - eg qualitative research - despite that they seem to infer clinical effectiveness from those studies.

Response: We have re-worded and simplified the interpretation of the statistic. We changed the wording to:
'Figure 3 shows the meta-analysis for the RCTs, which was possible for four studies [33, 34, 37, 38]. There was an overall RR of 0.12 (95% CI: 0.12, 0.66), i.e. those who had manual therapy had an 88% reduced risk of having an adverse event compared to those who did not have manual therapy (see Figure 3).'

We used a random effects model as indicated on the forest plots. We have added the following text to the methods section to be more explicit:
'Analyses

We aimed to meta-analyse data for RCTs and matched or paired cohort studies. For RCTs, we planned to extract final value scores for each group and convert them to standardised mean differences (SMD) and weighted mean differences for comparison using a random effects model due to the expected differences in treatment protocols and effects between studies.'

Comment: The strategy for selecting the paper is unusual as 2 teams by 2 people increase significantly the chance of producing bias. Then it is unclear how the arbiter (aka third reviewer in the paper) dealt with paper inclusion discussion. Usually the arbiter is external to the reviewers. Plus, for consistency and transparency, there is the need to state what were the papers discussed.
I challenge the reviewer's assumption that this would 'increase significantly the chance of producing bias'. It is not unusual in reviews with large numbers of papers to have multiple teams of researchers selecting and rejecting manuscripts. In reality the arbiters in the different teams ensured more consistency in decision making: discussion about borderline or confusing papers were challenged between the teams which meant there was little scope for complacency and more rigour as decisions had to be justified to the wider team. Final reasons for rejections are shown in the flow chart.

Authors meant to include all the languages but eventually they excluded just one Chinese paper (for language issue) but then in the discussion they argued that several research from China were took into consideration. This needs to be addressed as per consistency and clarity.

Response: We reviewed all titles and abstracts of the Chinese papers we found (these were in English), but only one Chinese paper abstract was selected for full paper review (written in Chinese). We have changed the text in the discussion to fully explain why the Chinese paper was rejected. 'This was a comprehensive and rigorously conducted review that included studies in all languages, including a growing number of articles published from China (titles and abstract were in English for indexing). There was one Chinese paper that was selected for full paper review. We translated this article but we were unable to fully interpret and understand the treatment given and the outcomes which related to Chinese Traditional Medicine energy points. In other words, the therapeutic paradigm presented was beyond our knowledge from a Western medicine perspective.'

Minor revisions: some misspelled words and parts of the paper that need revision

Reviewer: 3
Reviewer Name: Serge Brand
Institution and Country: University of Basel, Psychiatric Clinics (UPK)
Competing Interests: no competing interests

Comment: The authors present a systematic review of manual therapies to treat infants' excessive crying behavior and showed that the overall influence of manual therapies is moderate to mixed. The topic is interesting and important.
I suggest to expanding the introduction section: First, crying is almost the infants' only means to signaling needs to caregivers. Accordingly, second, excessive crying is considered the upper end of the range of early developmental crying behavior. Third, excessive crying seems to be unrelated to parents' behavior and parents' cultural background (St James-Roberts et al 2006, Pediatrics; Talachian et al 2008 World J Gastroenterol). Fourth, excessive crying is regarded as reflecting individual differences in maturation of the central nervous system (Barr 2002 Arch Pediatr Adol Med). Accordingly, fifth, in most cases, excessive crying is not related to gastrointestinal issues.
„Many aetiological factors for unsettled infant behaviour have been explored including digestive, musculoskeletal, breastfeeding and parenting problems [8-22]"; please, be more specific with this statement; clearly indicate which references do refer to which problem.
Given the methodological importance of Ref 23, I suggest to describing the content and the result of that publication in more details.
The systematic review has been conducted following the standards.
Conclusions are rigorously based on the extracted data.

Response: We used a large number of references to illustrate the extent of enquiry rather than suggest causes as there is considerable debate and opinion in this field. We have utilised the references the reviewer gave (new references15, 17, 19) and assigned the reference numbers after each potential aetiological factor and slightly changed the wording to:
Many aetiological factors for unsettled infant behaviour have been explored including diet, feeding and digestive issues [8, 9, 10, 11], musculoskeletal strains and disorders [12, 13,], developmental progress [14, 15, 16, 17] and parenting [18, 19, 20, 21, 22]. Despite extensive research, causative factors and effective treatment remain elusive.
We have added more information about the Dobson et al review [23] in the Introduction and the Discussion. Please see text added to the Introduction below and that shown in the Editors section and

Reviewer 2 section.
‘Other analyses showed a small beneficial effect for sleep but not for ‘recovery’. The studies included in this review were generally small and methodologically prone to bias, so definitive conclusions could not be drawn and effects were downgraded accordingly [23].’

Reviewer: 4
Reviewer Name: Nai Ming Lai
Institution and Country: Taylor's University, Malaysia
Competing Interests: None declared

Comment: This is a well-conducted systematic review and meta-analysis that attempted to update a recent Cochrane review on the same topic, with broader inclusion criteria of non-randomised studies aiming to include more parent-reported outcomes and reports of adverse events, although there were not much important new information to add from those non-randomised studies. Nonetheless, this updated review is important as it highlights the existing gaps in literature that assess parent-reported outcomes and parent-infant psychosocial assessments. Overall, the manuscript is well-written and easy to read, although I would have expected more specific details in the way of recommendations for future research, especially non-randomised trials, in particular specific outcomes to be evaluated (including recommended measuring tools such as scales) or scope of related qualitative studies, since these were the types of studies that the authors attempted to incorporate to get a richer perspective on the benefits and perception on manual therapy.

Below are some additional minor comments relating to specific parts of the manuscript:
Abstract, results: adverse effects should be reported comparatively (manual therapy versus control). At present it is only reported in the group that received manual therapy.

We added the following to the results section:
Conversely there were 11 non-serious adverse events in the infants not exposed to manual therapy (n= 97) giving an incidence rate of around 110 per 1,000 infants.
And the following to the abstract:
The risk of reported adverse events was low: 7 non-serious events per 1,000 infants exposed to manual therapy (n= 1308) and 110 per 1,000 in those not exposed.

Main text. Methods, Strength of evidence: What were the specific criteria to judge whether the conclusions were likely or unlikely to be affected by future studies?

Response: The section ‘Strength of evidence’ in the method explains that this is related to the quality of the studies and the consistency of the results between the studies.

Results, reduction in crying time: I suggest the authors present the results after limiting studies to parent-blinded studies, as in the recent Cochrane review.

Response: These results for crying time are exactly the same as those results presented in the Dobson et al review. However we have now introduced some text into the discussion section to consider this point.
‘Dobson et al (2012) conducted a sensitivity meta-analysis to explore parent blinding to their infant’s treatment (Miller et al (2012) [34] and Olafsdottir et al (2001) [36]) and interestingly their results showed there was no difference in crying time between groups with blinding.’

Figure 2: I square is 69%, suggesting substantial heterogeneity, which seems to be contributed by a single study Olafsdottir 2001. Was there any exploration done on possible reasons that might have contributed to the heterogeneity in the estimates?

Response: We have introduced this point to the discussion where we discuss heterogeneity in more detail. Please see text in the section for reviewer 2 who also raised some points about the I2 statistics.

Adverse events: the authors included "worsening symptoms" as part of the adverse events which I query. I would have thought worsening symptoms is part of the main outcome that related to the effectiveness (or "ineffectiveness") of the intervention assessed, and not adverse effects (which is usually unexpected). Please consider addressing this.

Response: We added the following text in the Discussion under the sub- title Safety:
'The safety data we extracted regarding adverse events indicated that manual therapy is a relatively low risk intervention, reflecting similar findings in other studies [24]. The definitions of adverse events recorded in the studies reviewed ranged from 'worsening symptoms' to seeking other forms of care: a comprehensive prospective cohort study specifically focused on adverse events in children is necessary to draw better conclusions.'

Reviewer: 5
Reviewer Name: Dr Viswas Chhapola
Institution and Country: Lady Hardinge Medical College, New Delhi, India
Competing Interests: None

Authors have attempted to perform a comprehensive literature search and performed the meta-analysis using both RCT and observational studies. There are few points on which the manuscript needs improvement

1. Authors should use PRISMA for abstract guideline to write the abstract.
2. Authors have followed most of steps of conducting a systematic review and meta-analysis.
3. The meta-analysis has studies which are similar to studies by Dobson et al. No new studies were available for inclusion in quantitative meta-analysis. So the conclusions are not expected to be any different either. The more important strength of current met-analysis should be the inclusion of observational studies. Authors have well summarised the observational studies in tables. However, a strong qualitative synthesis of observational studies has not been done. Authors should strengthen the qualitative synthesis of observational studies which they were not able to include in meta-analysis. The conclusions should be drawn on basis of both quantitative and qualitative synthesis. For guidance on conducting qualitative synthesis the authors should consult the publication from National academies press entitled "Finding What Works in Health Care: Standards for Systematic Reviews"

Responses:
1. We have used the PRISMA abstract guidance to inform the structure and content of the abstract, please see the new additions to the abstract.
3. There were new studies but it was not possible to include them in the effectiveness meta-analysis due to the outcomes reported. Please see the amended discussion which addresses the issue of additional value of this review compared to the Dobson et al review and the new section in the discussion on the non-RCT studies as suggested. The new text is shown in the editor response section.
We only had one qualitative study so a meta-synthesis of qualitative data was not possible. We conducted a narrative review of other studies, so have made this clearer in the methods section.
'For non-RCTs studies, analyses proposed were descriptive and narrative but change scores and RRs were extracted where possible. If there were a sufficient number of qualitative studies, we proposed to organise and synthesise findings from the qualitative data, by identifying emergent themes and sub-themes.

VERSION 2 – REVIEW

REVIEWER	Hilary Abbey, Head of Research The University College of Osteopathy, 275 Borough High Street, London SE1 1JE, UK
REVIEW RETURNED	17-Oct-2017

GENERAL COMMENTS	Reviewers' comments have been addressed.

REVIEWER	Francesco Cerritelli University of Chieti-Pescara, Italy
REVIEW RETURNED	06-Nov-2017

GENERAL COMMENTS	Thank you for addressing the majority of the previous concerns. The manuscript improved significantly. My only concern is related to the meta-analysis that was presented. I understand that the authors wanted to pull the data but the studies included are largely heterogeneous (see the statistical heterogeneity but also the methodological and clinical heterogeneity). This, therefore, might lead to biased, imprecise paper conclusions. My suggestion, as in the previous review, is to avoid pulling the data (not to run the meta-analysis) and maintain the SR only.

REVIEWER	Serge Brand University of Basel, Psychiatric Clinics (UPK)
REVIEW RETURNED	22-Oct-2017

GENERAL COMMENTS	The authors addressed well the issues raised by the reviewers. The manuscript improved and is an important contribution to the current literature.

REVIEWER	Nai Ming Lai Taylor's University, Malaysia
REVIEW RETURNED	13-Oct-2017

GENERAL COMMENTS	The authors have taken great efforts to address all reviewers' comments, and as far as I am concerned, they have made sufficient improvement to the manuscript given its limitations to justify its place to the potential readers.

REVIEWER	Dr Viswas Chhapola Kalawati Saran Children's Hospital & Lady Hardinge Medical College , New Delhi
REVIEW RETURNED	31-Oct-2017

GENERAL COMMENTS	Authors have made the necessary changes in manuscript. Manuscript looks in good flow now.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Hilary Abbey, Head of Research
Institution and Country: The University College of Osteopathy, 275 Borough High Street, London SE1 1JE, UK
Competing Interests: None declared

Reviewers' comments have been addressed.

Reviewer: 2
Reviewer Name: Francesco Cerritelli
Institution and Country: University of Chieti-Pescara, Italy
Competing Interests: None declared

Comment: Thank you for addressing the majority of the previous concerns. The manuscript improved significantly. My only concern is related to the meta-analysis that was presented. I understand that the authors wanted to pull the data but the studies included are largely heterogeneous (see the statistical heterogeneity but also the methodological and clinical heterogeneity). This, therefore, might lead to biased, imprecise paper conclusions. My suggestion, as in the previous review, is to avoid pulling the data (not to run the meta-analysis) and maintain the SR only.

Response: Despite the high I2 we still decided to pool the data because the heterogeneity can be attributed mainly to one study (Olafsdottir et al 2001) and the other studies had confidence intervals that showed considerable overlap.

The meta-analysis clearly shows the reader graphically (and therefore illustrates the points nicely) the outlier contributing most to the heterogeneity (Olafsdottir et al 2001). We would suggest that a narrative analysis could be potentially more biased and imprecise but in this case we would come to the same conclusion, i.e. some small benefit for crying time overall but whether these are clinically meaningful for parents and the mechanism of actions remain unclear.

We understand that the reviewer has concerns about pooling the data but as stated in the previous response the decision to pool and present data is multi-faceted. We have already included in the discussion issues around methodology and that in a clinical sense we still cannot determine what the active mechanisms of action are. We state clearly that the manual therapy component may not be the active element of the intervention but the non-specific effects of the total consultation and patient – practitioner contact. We have moderated our conclusions accordingly.

Whilst Cochrane make recommendations about levels of heterogeneity, so do Higgins et al 2003, neither suggest absolutes.

In the light of reviewer 2 comments we have moderated and modified the discussion and conclusions even further.

In the discussion:
‘The I2 statistic in our meta-analysis and Dobson et al’s (2014) were 69% and 55% respectively, indicating heterogeneity between the studies analysed. This was not unexpected due to the potential variation in treatments (and hence effects), loose diagnostic criteria and the power of the samples for the RCTs. Therefore, the results have to be considered with caution and are likely to change with

further research. The meta-analysis helps illustrate and indicate that future research in this field requires well powered studies, flexible but protocolised treatment and parental blinding.'

In the conclusion:
'We found moderate favourable evidence for the reduction in crying time in infants receiving manual therapy care (around one hour per day), but this may change with further research evidence. We still do not know if this result is meaningful to parents or if the reduction is due to the manual therapy component of care or other aspects of care. For other outcomes the strength of evidence was low and inconclusive.'

Reviewer: 3
Reviewer Name: Serge Brand
Institution and Country: University of Basel, Psychiatric Clinics (UPK)
Competing Interests: no competing interests.

The authors addressed well the issues raised by the reviewers. The manuscript improved and is an important contribution to the current literature.

Reviewer: 4
Reviewer Name: Nai Ming Lai
Institution and Country: Taylor's University, Malaysia
Competing Interests: None declared

The authors have taken great efforts to address all reviewers' comments, and as far as I am concerned, they have made sufficient improvement to the manuscript given its limitations to justify its place to the potential readers.

Reviewer: 5
Reviewer Name: Dr Viswas Chhapola
Institution and Country: Kalawati Saran Children's Hospital & Lady Hardinge Medical College , New Delhi, India
Competing Interests: None declared

Authors have made the necessary changes in manuscript. Manuscript looks in good flow now.