

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Conservative care with or without manipulative therapy in the management of back and/or neck pain in Danish children aged 9-15: a randomized controlled trial nested in a school-based cohort
AUTHORS	Dissing, Kristina; Hartvigsen, Jan; Wedderkopp, Niels; Hestbaek, Lise

VERSION 1 – REVIEW

REVIEWER	César Fernández-de-las-Peñas Universidad Rey Juan Carlos
REVIEW RETURNED	13-Jan-2018

GENERAL COMMENTS	<p>The introduction should include a brief introduction of the relevance of spinal pain in children and the particularities of this population in relation to spinal pain on adults. This study covers a relevant topic but there are several flaws. Although it is important to conduct a pragmatic RCT, the problem is the inconsistent in the approaches and the professionals treating the children. There is no rational for doing any manipulation, so this can explain the lack of differences. One thing is doing a pragmatic, more realistic RCT, other thing is doing what clinicians want without rational</p> <p>The main outcome is too broad.. Spinal pain recurrence, can include small pain, different intensity, longer or shorter duration, in the same place of the spine. Etc..</p> <p>In the results, I do not understand a range of 1 and 800 days of follow-up. This is highly confusing</p>
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REVIEWER	Michael Masaracchio, PT, PhD, OCS, SCS, FAAOMPT Long Island University Department of Physical Therapy, USA
REVIEW RETURNED	17-Jan-2018

GENERAL COMMENTS	<p>Introduction</p> <p>Line 16: would suggest various healthcare professionals" It is the individuals who perform the treatment, not the profession.</p> <p>Line 20: the phrase children's health" I would consider changing this phrase. This too broad of a statement and it appears this study only consider spinal pain, so I am suggesting a rewrite of this sentence. One possible suggestion is musculoskeletal dysfunction.</p> <p>Line 27-34: these sentences are important and therefore need to be re-written in a stronger manner to strengthen the introduction. In fact, this is the most problematic area with this manuscript. The authors should be commended on the statistical analysis, results, and discussion section. I suggest that the introduction be expanded upon to include other research and make a stronger argument for</p>
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	<p>the need of the study.</p> <p>Methods: Line 29-31 the title mentions spinal pain but in various sections in the methodology it talks about extremity complaints. I am a little confused why this is being mentioned in this study. Correct me if I am wrong, but this study was assessing neck and/or back pain. I think mentioning extremity symptoms confuses the reader. Please clarify any place this is mentioned, or take it out completely. With the language of manipulation and mobilization being so confusing to everyone, I would suggest operationally defining these terms so it is clear to all readers especially with the pragmatic design of this RCT.</p> <p>Interventions: Line 48: I commend the authors on their choice of a pragmatic design. This is more common in RCT now, as it resembles clinical practice more closely. The choice of interventions was decided by each treating chiropractor based on biomechanical assessment and pain provocation. I strongly suggest a paragraph in the discussion about the current research and its support of deciding manual therapy interventions based on biomechanical assessments, versus pain provocation. The majority of research states that biomechanical assessment is not reliable and therefore may not lead to appropriate interventions. Therefore I think a discussion of this is necessary in the discussion section briefly. Also, perhaps this is an area that can be expanded upon in the introduction but explaining the mechanisms of manual therapy a bit to augment the purpose of this manuscript.</p> <p>Results: the authors should be commended on their results section, statistical analysis, and presentation of the results. Well done. As it relates to harm, I would encourage an operational definition and specify the difference between adverse events and transient side effects. (Puenedura et al, 2015 Journal of Manual and Manipulative Therapy) Title: Safety of thrust manipulation in the thoracic spine.</p> <p>Any other feedback I would have suggested was addressed in the limitation section of this manuscript. I believe the authors make some compelling arguments for why the results panned out the way they did and also have made nice suggestions for future research.</p> <p>Lastly, kudos on the previous RCT that was published. Treatment of spinal pain in children is needed, and this area of research needs to be expanded upon in clinical practice. This is difficult to do and the authors should be commended for this line of inquiry.</p>
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REVIEWER	Michele Maiers Northwestern Health Sciences University, United States of America
REVIEW RETURNED	29-Jan-2018

GENERAL COMMENTS	<p>Thank you for this research and the opportunity to review this paper. Pediatric response to manipulative therapies deserves greater focus within the spine care community, and this pragmatic trial is an important contribution to that effort.</p> <p>Overall, the paper is well written. There are a few items that were unclear to this reader, and some revisions the team may want to consider to strengthen this work:</p> <ol style="list-style-type: none"> 1. who delivered the advice, exercise and soft tissue treatment for each group? Was it the same group of providers who delivered the
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	<p>manipulation (chiropractors)?</p> <p>2. who indicated the level of pain (children themselves, or their parents), and was this only collected during visits (self report or reported through the provider), or via SMS? This information seems to be missing in the primary paper. From the protocol paper, I infer that pain ratings were collected during visits only, but I am unsure. At a minimum, this should be clarified in the primary paper. It may also present limitations worth discussing.</p> <p>3. Is there data to report on the number and frequency of visits? Compliance with exercise recommendations?</p> <p>4. What percent of children were referred to secondary care spine center for second opinion, as per the protocol? Did you collect any data on additional care sought?</p> <p>5. The most significant limitation to this work is the inability to distinguish whether the spinal complaint referred to in the SMS weekly response is the same complaint that the child initially presented with/ had treated. This is briefly mentioned in the discussion, but I feel warrants more extensive discussion since it is not uncommon for children to have multiple concurrent spinal complaints, "text neck", etc.</p>
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REVIEWER	Aaron Yaras Optum Patient Insight, USA
REVIEW RETURNED	28-Mar-2018

GENERAL COMMENTS	<p>The authors indicated substantial missing data, but their scheme for substitution of missing data (assume that all missing scores between "1s" were also "1") seems simplistic and not realistic. I also don't know that i agree their SMS response likelihood would be missing at random; i can see that parents would be more likely to report presence of a symptom than absence. Thus, I would request that the authors conduct sensitivity analyses on their primary outcome and related secondary outcomes in which missing values are replaced as follows:</p> <ol style="list-style-type: none"> 1. All missing values set to 0 2. Missing values imputed as a function of non-missing values and key covariates (assuming MAR is in fact the case).
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: César Fernández-de-las-Peñas Institution and Country: Universidad Rey Juan Carlos Please state any competing interests or state 'None declared': None declared

The introduction should include a brief introduction of the relevance of spinal pain in children and the particularities of this population in relation to spinal pain on adults.

The introduction has been rewritten and now reads:

Spinal pain is prevalent in youth and reaches adult levels already around the age of 18¹, but it is transient and inconsequential for most children. Therefore it has largely been ignored in research, but some children have frequent, recurrent and bothersome complaints²⁻⁵, which impact mental wellbeing⁶ and have the potential to decrease the level of physical activity. Importantly, these problems seem to track into adulthood, i.e. the most affected adolescents grow up to be the most affected adults^{7,8}. Therefore,

proper management at an early stage is essential to improve lifetime trajectories of spinal pain.

Management of children's musculoskeletal disorders relies to a large extent on parents' values, preferences and experience, and due to absence of guidelines for the treatment of spinal pain in children, healthcare professionals have to rely on guidelines developed for adults⁹.

Manipulative therapy (MT) is defined as joint manipulation and/or mobilization with the aim to restore compromised function of joints. This type of therapy is increasingly being used in children¹⁰⁻¹² because it is generally recommended as a treatment option for adults with spinal pain¹³⁻¹⁷, and is delivered by various health professions, both on its own and in combination with other types of therapy, such as advice, exercises, and soft tissue treatment¹⁷. One study recently demonstrated a small but statistically significant effect of adding SMT to exercise therapy¹⁸ in adolescents with low back pain. However this is the only full scale randomized controlled trial (RCT) conducted to date to investigate the effect of SMT in children with any type of spinal pain^{9,19}.

The aim of this pragmatic randomized controlled trial was to determine the effectiveness of adding manipulative therapy to other conservative care (advice, exercises and soft tissue treatment) on the number of recurrences of spinal pain in children aged 9 to 15 years who were participating in a school-based open cohort study. Secondary outcomes included the short-term effect on duration of spinal pain episodes, pain intensity, and Global Perceived Effect.

This study covers a relevant topic but there are several flaws. Although it is important to conduct a pragmatic RCT, the problem is the inconsistent in the approaches and the professionals treating the children. There is no rationale for doing any manipulation, so this can explain the lack of differences. One thing is doing a pragmatic, more realistic RCT, other thing is doing what clinicians want without rationale

We agree that the different approaches and the inconsistencies among professionals is a major problem in the treatment of musculoskeletal problems in children (as well as in adults). Therefore, research into the different approaches is strongly needed and this manuscript can hopefully add to this evidence base.

The rationale for using manipulative treatment in children is the same as in adults: to restore/normalize joint mobility and this has been added both to the introduction and the methods.

The main outcome is too broad.. Spinal pain recurrence, can include small pain, different intensity, longer or shorter duration, in the same place of the spine. Etc..

It is true that the choice of primary outcome is controversial and poses some challenges with regard to interpretation. We have added a paragraph about this interpretation in the discussion under a new subheading 'Choice of outcome':

"We originally intended to analyze the three spinal regions separately, however the pain site could change within the same individual during follow up, and many individuals reported pain from several regions. Therefore, the interpretation of our results relate to 'spinal pain' as a coherent entity. We could not determine by the SMS answers whether recurrences were actual recurrences of the same problem at the same location in the spine, but simply conclude that there was subsequent spine-related pain. This can be considered a weakness as we cannot determine true recurrences; however it can also be considered to be a strength because pain in this age group appears to demonstrate a shift between regions of the spine over time, indicating that there is not independence between pain in the three regions (REF)."

The paragraph following this in the discussion relates to pain intensity; and with respect to duration, this is illustrated in the sensitivity analysis.

In the results, I do not understand a range of 1 and 800 days of follow-up. This is highly confusing. The definition of follow-up length is "Number of days between inclusion date and last SMS". This has been added:

“Follow-up time was defined as “Number of days between inclusion date and last SMS”. Since one child left the study the day after inclusion, this resulted in 1 to 868 follow-up days,”

One student answered a follow-up SMS one day after inclusion and then left the study. As the results are based on intention-to-treat analyses, this outlier is included. If he was excluded, the range would be 75 to 800 days.

Reviewer: 2

Reviewer Name: Michael Masaracchio, PT, PhD, OCS, SCS, FAAOMPT Institution and Country: Long Island University, Department of Physical Therapy, USA Please state any competing interests or state ‘None declared’: None declared

Introduction Line 16: would suggest various healthcare professionals" It is the individuals who perform the treatment, not the profession.

Agree – this has been changed

Line 20: the phrase children's health" I would consider changing this phrase. This too broad of a statement and it appears this study only consider spinal pain, so I am suggesting a rewrite of this sentence. One possible suggestion is musculoskeletal dysfunction.

Agree – this has been changed to “Management of musculoskeletal disorders in children relies....”

Line 27-34: these sentences are important and therefore need to be re-written in a stronger manner to strengthen the introduction. In fact, this is the most problematic area with this manuscript. The authors should be commended on the statistical analysis, results, and discussion section. I suggest that the introduction be expanded upon to include other research and make a stronger argument for the need of the study.

The introduction has been rewritten and now reads:

Spinal pain is prevalent in youth and reaches adult levels already around the age of 18¹, but it is transient and inconsequential for most children. Therefore it has largely been ignored in research, but some children have frequent, recurrent and bothersome complaints²⁻⁵, which impact mental wellbeing⁶ and have the potential to decrease the level of physical activity. Importantly, these problems seem to track into adulthood, i.e. the most affected adolescents grow up to be the most affected adults^{7,8}. Therefore, proper management at an early stage is essential to improve lifetime trajectories of spinal pain.

Management of children’s musculoskeletal disorders relies to a large extent on parents’ values, preferences and experience, and due to absence of guidelines for the treatment of spinal pain in children, healthcare professionals have to rely on guidelines developed for adults⁹.

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The aim of this pragmatic randomized controlled trial was to determine the effectiveness of adding manipulative therapy to other conservative care (advice, exercises and soft tissue treatment) on the number of recurrences of spinal pain in children aged 9 to 15 years who were participating in a school-based open cohort study. Secondary outcomes included the short-term effect on duration of spinal pain episodes, pain intensity, and Global Perceived Effect.

Methods:

Line 29-31 the title mentions spinal pain but in various sections in the methodology it talks about extremity complaints. I am a little confused why this is being mentioned in this study. Correct me if I am wrong, but this study was assessing neck and/or back pain. I think mentioning extremity symptoms confuses the reader. Please clarify any place this is mentioned, or take it out completely. *We can see how this could be confusing. Children in the MT group also received MT to the extremities if indicated, whereas the children in the MT group did not. We have clarified this by adding "If the child experienced any pain the extremities during the study period, these were also treated with manipulative therapy at the discretion of the treating chiropractor" to the description of the intervention and deleted all references to extremity symptoms in the rest of the manuscript.*

With the language of manipulation and mobilization being so confusing to everyone, I would suggest operationally defining these terms so it is clear to all readers especially with the pragmatic design of this RCT.

This is a good point also referred to by the editor. In the description of the intervention, we have added:

"Manipulative therapy was defined as high velocity, low amplitude manipulation and/or mobilization of the joints to restore segmental spinal motion."

Interventions:

Line 48: I commend the authors on their choice of a pragmatic design. This is more common in RCT now, as it resembles clinical practice more closely. The choice of interventions was decided by each treating chiropractor based on biomechanical assessment and pain provocation. I strongly suggest a paragraph in the discussion about the current research and its support of deciding manual therapy interventions based on biomechanical assessments, versus pain provocation. The majority of research states that biomechanical assessment is not reliable and therefore may not lead to appropriate interventions. Therefore I think a discussion of this is necessary in the discussion section briefly.

This is a good point, but since we already have exceeded the recommended word limit, we chose to add a sentence and a reference about this to the description rather than a paragraph in the discussion. The description now reads:

"Manipulative therapy was delivered at the discretion of the chiropractor and applied on the basis of a combination of biomechanical dysfunction and pain provocation responses found during the clinical examination of the child²⁵, since palpatory findings by itself have been found unreliable (REF)."

Also, perhaps this is an area that can be expanded upon in the introduction but explaining the mechanisms of manual therapy a bit to augment the purpose of this manuscript.

This has been included in the new introduction

Results: the authors should be commended on their results section, statistical analysis, and presentation of the results. Well done.

As it relates to harm, I would encourage an operational definition and specify the difference between adverse events and transient side effects. (Puenedura et al, 2015 Journal of Manual and Manipulative Therapy) Title: Safety of thrust manipulation in the thoracic spine.

The paragraph about 'harms' has been changed as suggested and now reads:

"Adverse events can be defined as the sequelae following manipulative therapy to the spine that are medium to long term in duration, with moderate to severe symptoms, and of a nature that is serious, distressing and unacceptable to the patient and requires further treatment²⁶. To our knowledge, no adverse events following manipulative therapy have been reported in children of this age group^{27,28}. However, it is common to experience transient side effects such as temporary reddening or soreness in the area being treated after both soft tissue treatment and manipulative therapy²⁹. Treating chiropractors recorded transient side effects if the child stated these at the consultation, but none were reported. No children were referred to other health care providers, including general practitioners, because of adverse events."

Any other feedback I would have suggested was addressed in the limitation section of this manuscript. I believe the authors make some compelling arguments for why the results panned out the way they did and also have made nice suggestions for future research.

Lastly, kudos on the previous RCT that was published. Treatment of spinal pain in children is needed, and this area of research needs to be expanded upon in clinical practice. This is difficult to do and the authors should be commended for this line of inquiry.

Thank you

Reviewer: 3

Reviewer Name: Michele Maiers

Institution and Country: Northwestern Health Sciences University, United States of America Please state any competing interests or state 'None declared': None declared

Thank you for this research and the opportunity to review this paper. Pediatric response to manipulative therapies deserves greater focus within the spine care community, and this pragmatic trial is an important contribution to that effort.

Overall, the paper is well written. There are a few items that were unclear to this reader, and some revisions the team may want to consider to strengthen this work:

1. who delivered the advice, exercise and soft tissue treatment for each group? Was it the same group of providers who delivered the manipulation (chiropractors)?

This has been clarified by adding "Both groups were treated by the RCT team consisting of seven chiropractors." in the description of the intervention.

2. who indicated the level of pain (children themselves, or their parents), and was this only collected during visits (self report or reported through the provider), or via SMS? This information seems to be missing in the primary paper. From the protocol paper, I infer that pain ratings were collected during visits only, but I am unsure. At a minimum, this should be clarified in the primary paper. It may also present limitations worth discussing.

Good point. We have added this to inclusion criteria in Table 1, so it now reads: "Pain in neck or back equal to or greater than 3 on an 11-box numerical rating scale for more than three days indicated by the child at the first visit"

3. Is there data to report on the number and frequency of visits? Compliance with exercise recommendations?

The children in the MT group had 1330 clinical contacts (mean 16.8 (95%CI: 16.3-17.3)) vs. 1108 (mean 15.3 (95%CI: 14.7-15.9)) in the non-MT group. However, these data (files from follow-up consultations) are not validated and we are concerned that they might be incomplete, as reflected by the poor response rate of the practitioner reported follow-up outcomes (NRS at two weeks etc.).

Therefore, and because there are no economic evaluation intended in the study, we decided to leave it out.

Unfortunately there is no data on exercise compliance.

4. What percent of children were referred to secondary care spine center for second opinion, as per the protocol? Did you collect any data on additional care sought?

Unfortunately, this information was not collected. This will definitely be included in future studies.

5. The most significant limitation to this work is the inability to distinguish whether the spinal complaint referred to in the SMS weekly response is the same complaint that the child initially presented with/ had treated. This is briefly mentioned in the discussion, but I feel warrants more extensive discussion since it is not uncommon for children to have multiple concurrent spinal complaints, "text neck", etc. You are absolutely right. We have added a paragraph about this interpretation in the discussion under a new subheading 'Choice of outcome':

"We originally intended to analyze the three spinal regions separately, however the pain site could change within the same individual during follow up, and many individuals reported pain from several regions. Therefore, the interpretation of our results relate to 'spinal pain' as a coherent entity. We could not determine by the SMS

answers whether recurrences were actual recurrences of the same problem at the same location in the spine, but simply conclude that there was subsequent spine-related pain. This can be considered a weakness as we cannot determine true recurrences; however it can also be considered to be a strength because pain in this age group appears to demonstrate a shift between regions of the spine over time, indicating that there is not independence between pain in the three regions (REF)."

The paragraph following this in the discussion relates to pain intensity; and with respect to duration, this is illustrated in the sensitivity analysis.

Reviewer: 4

Reviewer Name: Aaron Yaras

Institution and Country: Optum Patient Insight, USA Please state any competing interests or state 'None declared': None declared

The authors indicated substantial missing data, but their scheme for substitution of missing data (assume that all missing scores between "1s" were also "1") seems simplistic and not realistic. I also don't know that i agree their SMS response likelihood would be missing at random; i can see that parents would be more likely to report presence of a symptom than absence. Thus, I would request that the authors conduct sensitivity analyses on their primary outcome and related secondary outcomes in which missing values are replaced as follows:

1. All missing values set to 0
2. Missing values imputed as a function of non-missing values and key covariates (assuming MAR is in fact the case).

We agree that the choice of substituting data can have strong implications and this is only briefly touched upon in this manuscript. However, we have performed more extensive sensitivity analyses previously on the same data which is referred to in the present manuscript (ref. 25). To limit the size of this paper we chose to refer to these previous analyses in this manuscript. This has now been emphasized by adding:

"Since this type of outcome measure has not been used in previous trials, there is no consensus on how to substitute data. In a previous article we have described the consequences of different data substitution strategies³"

Extract from the previous article (ref 3):

"Missing SMS responses had an impact on how to determine the length of an episode because it was impossible to determine if the child still had spinal pain or was pain-free in the week with the missing answer. We therefore formulated two decisions rules for defining the end of an episode. The first was if there were four or fewer consecutive missing answers, preceded and followed by a '1', then this was considered as one continuous episode and the missing values were imputed as '1'. The second was if there were more than four consecutive missing answers, or the next answer after missing was '2', '3' or '4', we considered the episode of spinal pain as terminated by the last report of '1'.

Because there is no literature to support this decision, a sensitivity analyses was performed to estimate the impact of this decision. For that purpose, the missing weeks were treated in two extreme ways: first, we imputed the missing answers to be the same as the last answer, regardless of the value of the next report. This would potentially inflate the episode lengths and diminish the number of episodes. Second, we imputed an answer of '4' (no pain) for all the weeks with missing answers, which would do the opposite. Thereby, we determined the range within which the correct answer would likely lie.

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Results of the sensitivity analysis assessing the impact of missing data showed no differences between the three different types of imputation in relation to number and lengths of episodes (Table 6).

Table 6 Sensitivity analyses on missing data

	Primary data				v1 data				v2 data			
	Median number of episodes (IQR)	Mean number of episodes (SD)	Median length of episodes (IQR)	Mean length of episodes (SD)	Median number of episodes (IQR)	Mean number of episodes (SD)	Median length of episodes (IQR)	Mean length of episodes (SD)	Median number of episodes (IQR)	Mean number of episodes (SD)	Median length of episodes (IQR)	Mean length of episodes (SD)
Study year 1	1 (1-2)	1.9 (1.4)	1 (1-3)	2.6 (2.9)	1 (1-2)	1.9 (1.4)	1 (1-3)	2.6 (2.9)	1 (1-2)	2.0 (1.5)	1 (1-3)	2.7 (3.0)
Study year 2	1 (1-2)	1.9 (1.6)	1 (1-3)	2.9 (3.3)	1 (1-2)	1.9 (1.6)	1 (1-3)	2.9 (3.3)	1 (1-2)	2.0 (1.7)	1 (1-3)	2.9 (3.3)
Study year 3	1 (1-2.5)	2.0 (1.4)	1 (1-3)	3.0 (3.3)	1 (1-3)	2.0 (1.4)	2 (1-3)	3.0 (3.3)	1 (1-3)	2.1 (1.5)	2 (1-4)	3.0 (3.3)

- Primary data: up til 4 missing weeks after a '1' is imputed with '1'
- v1: all missing weeks after a '1' is imputed with '1'
- v2: all missing weeks after a '1' is imputed with '4'

Defining a new episode as starting after four weeks of 'no pain' instead of one week, resulted in a reduction of number of episodes by 20.0%, 18.8% and 18.0% in study years 1, 2 and 3 respectively, and the maximum number of episodes decreased from 8 to 5, 12 to 6 and 9 to 6 in study years 1, 2 and 3 respectively. No difference in the median number of episodes was found and the mean number was only slightly smaller (1.9 to 1.5), with a higher proportion of children having 1 or 2 episodes.

Finally, we found somewhat higher proportion of episodes lasting for one week, (62.0%, 59.1% and 53.2% vs 59.1%, 56.6% and 51.2% for study year 1, 2 and 3 respectively), but overall, the distribution between the different lengths of episodes was almost the same.

Reference: Dissing KB. Spinal pain in Danish school children – how often and how long? The CHAMPS Study-DK. *BMC musculoskeletal disorders* 2017 doi: 10.1186/s12891-017-1424-5

VERSION 2 – REVIEW

REVIEWER	Cesar Fernandez-de-las-Peñas Universidad Rey Juan Carlos, Spain
REVIEW RETURNED	08-May-2018

GENERAL COMMENTS	The authors have answered all my comments properly
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REVIEWER	Michael Masaracchio Long Island University, USA
REVIEW RETURNED	14-May-2018

GENERAL COMMENTS	<p>I would like to commend the authors for their work on this manuscript. The additions and explanations provided make this a much stronger manuscript for publication. I am very pleased with the additions in the introduction section. My only comment left is the grammatical syntax in the introduction, especially the first paragraph. This sets the tone for the rest of the paper, so please address the first three sentences which sound a bit awkward for lack of a better word.</p> <p>Also in the abstract start the sentence with Two hundred thirty eight, not 238.</p> <p>Thank you.</p>
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REVIEWER	Aaron Yaras Optum, USA
REVIEW RETURNED	23-May-2018

GENERAL COMMENTS	The authors have satisfactorily addressed my concerns.
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VERSION 2 – AUTHOR RESPONSE

Thank you for your positive response to this manuscript and for recommending it to publication.

I have made a minor revision as suggested in the introduction, and have changed the 238 in the abstract into words. However, it exceeds 300 words, and therefore I have left it as it is in the next step in this proces, but in the manuscript it has been changed.

I am very pleased with the reviewers suggestions and comments in this proces and I think it has made a great improvement on the final result.