PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Outcome and comparator choice in Molar Incisor Hypomineralization (MIH) Intervention Studies: A Systematic Review and Social Network Analysis
AUTHORS	Elhennawy, Karim; Krois, Joachim; Jost-Brinkmann, Paul-Georg; Schwendicke, Falk

VERSION 1 - REVIEW

REVIEWER	Juliana Feltrin de Souza Department of Stomatology Universidade Federal do paraná Brazil
REVIEW RETURNED	21-Jan-2019

GENERAL COMMENTS	This systematic review brings a fundamental discussion about the "Outcome and comparator choice" in clinical studies addressing Molar incisor hypomineralization. It is an original idea and valuable for future clinical studies focus on MIH. However, the paper brings a superficial discussion about the MIH and their outcomes and comparator choice. The idea of the "Core Outcome Measurement Instrument Sets" requires a deeper knowledge and discussion about the MIH and their outcomes.
	ABSTRACT:
	1. Describe "COS" it is the first time that its appear;
	2. Describe in the results section the SNA results; It is not clear the terms "clinically- and patient-centered Outcomes". In my point of view, it appears obvious. If you are evaluating the observational and clinical trials studies about the interventions in MIH, what others outcome could you expect?
	STRENGTHS AND LIMITATIONS OF THIS STUDY
	States the actual/true "Strengths and limitations of the study" and not repeat the objective of the study.
	INTRODUCTION
	Page 3 LINE 18: "also, researchers usually collected a range of outcomes, without necessarily reporting all of them later on. This may lead to selective reporting and introduce significant bias."

Explain the "and introduce significant bias". Could be the bais of unpublished data?

Page 3 Line 15 and 32 the term further stakeholders. Who are the "further stakeholders"? Line 32: Why you use the terms patient and further stakeholders? Are there others further stakeholders besides the patients?

Page 3 Paragraphs line48/54: Describe the clinical presentations and consequences of the MIH. This information are the fundamental point to justify your study, once it determines the variety of outcome and comparators.

Methods:

It is not clear if the terms "molar incisor hypomineralisation) OR molar incisor hypomineralization) OR mih" could include all studies with MIH. Because this term is after 2001, there are previous studies describing MIH with other terms such as "cheese molars". It could be a limitation of the study.

About the eligible criteria, it is not clear the exclusion aspects, language, studies design. For example, a case report is a design of the observational study, is it included? Is there language restriction?

Results:

Page 6 line 16: "A list of comparators was compiled and comparators grouped into agreed categories (Table 2)." The Table 2 describes the outcomes or comparators?

Page 6 Line 58: Please correct: "were incl10uded (Fig. 1)"

According described about the comparators analysis "Statistical analysis included the assessment of the degree (average number of comparators per node) and the clustering coefficient (values of one indicate that all possible connections were made, while values of 0, indicate that only the minimum number of connections were made)". Does it make sense to apply this analysis only in clinical study? Because in observational studies could be not performed comparations.

Page 8 line 3 "The cluster coefficient was 0.69, indicating that there were "cliques" of comparators present, with comparators being mainly compared within and not across these cliques. " Is there a cuff-off points of cluster coefficient and its interpretation? What is meaning "cliques"?

Page 9 1st paragraph: "The outcomes used in MIH intervention studies focused on two areas; restoration success (measured via the USPHS criteria or similar tools) and pain and hypersensitivity management (measured via scales like the Visual analogue scale or the Schiff Cold Air Sensitivity Scale). Combined, these two areas accounted for 45% of primary outcomes and for 50% of all reported outcomes." It is important discuss about it. Why is important this outcome, what is the differences in MIH?

It is a fundamental paragraph of the discussion, about the outcomes. Here, it was required to be involved with the context, MIH, describing the differences of outcome for molars and for incisors. In my opinion, the important outcome for both is the survival of the enamel until its breakdown or caries lesion or survival of the restoration clinically adequate, in other words, the success rate of remineralization or restoration. Please, discuss about this outcome, adding information about the difficulties of MIH managing.

Page 9 line 56 until page 10 line 17. "Our network analysis indicated a network with limited connectivity" What is a "good" rate of connectivity?? I think important add what do connectivity between the comparators indicate in terms of validity of the study? It is possible/ important measure "network connectivity" of studies with different objectives such as restoration success and improve the aesthetic appearance? For my it do not make sense. Please, add this information on discussion. Or measure the network connectivity according to the proposal of the primary study.

Page 11 line 10: "our SNA results implicate that current evidence may not be robust." Do only your analysis power to state it? Or Was it based on all methodological aspects of the primary study?

Figure 3: The network graph could be applied for molars and for incisor separately?

Add on the legend the mean of "PMC" and "CPP-ACP"

The terms "infiltration" and "conditioning" were comparators for clinical or observational studies?

Table 2: About the outcome "mineral gain" it was measured by Laserfluorescence readings
Scanning electron microscope (SEM)/
Energy Dispersive X-ray Spectrometry (EDX)
Quantitative Light-Induced Fluorescence (QLF)
SEM and EDX are applied on in vitro studies. It was performed on this clinical/observational studies?

REVIEWER	Mihiri Silva
	Inflammatory Origins,
	Murdoch Children's Research Institute
REVIEW RETURNED	12-Feb-2019

GENERAL COMMENTS	Reviewer comments
	Overall:
	This manuscript addresses an important issue in paediatrics and is a robust and well written contribution to the evidence base regarding the management of teeth affected by Molar Incisor Hypomineralisation. It is commended for its clear, rigorous methodology and meaningful discussion. This study is valuable not

only for its implications in terms of directing future studies of MIH but also for setting an excellent example of conducting research with a more holistic and patient centered focus. The manuscript does require close editing as there are a number of minor typographical errors.

Page 4, Line 19

"evaluating the relationships between actors"

Is this meant to read "evaluating the relationships between factors"?

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"Patients were not involved in this study at this point, but will so in the core outcomes
definition."

Please as 'do' between 'will' and 'so' ie "

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Typographical error, amend to "number of participants"

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Amend to either "In the remaining" or "in one other"

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"researchers tend to publish multiple from the same clinical trial"

Missing word, amend to :
"…researchers tend to publish multiple reports from the same clinical trial"

Page 10, Line 40-42
"However, data is then divided across multiple publications, and linking articles together or with registered protocols can be difficult"

The meaning of this sentence is not clear – is there as missing word?

REVIEWER	Roland Matsouaka
	Duke University, North Carolina, US
REVIEW RETURNED	21-Mar-2019

| GENERAL COMMENTS | In this paper, Elhennawy et al., propose to investigate different outcomes and comparators used in molecular incisor hypomineralization (MIH) studies to establish a list of core of the important tools. |

	Current studies in MIH use a wide range of outcomes and comparators, which make it difficult to know whether these studies : (1) report the results on all outcomes or comparators they collect or they pick and chose those that are aligned with the investigators narrative(s); (2) measure meaningful outcomes or comparators that can be compared or comparable across studies; (3) are meaningful to all stakeholders (patients, dentists, clinicians, researchers, regulatory agencies, insurance companies, etc.) Therefore, it is important to develop a core outcome set (COS) for MIH along with current comparators. This paper provide a review of outcomes used in MIH studies to inform such a development of COS. The objective of this study is clear and is of great significance. There are some major flaws/limitations I would like to point out: 1. Although the disease/condition, subject of this study, is named, there is nowhere in the manuscript where the authors have described the conditions, presented the symptoms/issues related to this conditions, or explained the rationale/driving force that lead investigators to use a wide range of outcomes and comparators for MIH. Although this might be obvious to the authors, this is not the case for all potential readers of the manuscript (including me). 2. The authors didn't provide the list of summary (statistical) measures that were used in the papers they evaluated. Making a recommendation of what outcomes to use should also allow future investigators to know which measures are important for reporting their findings. Providing summary measures is indeed the next to last item on the PRISMA 2009 Checklist. Unfortunately, the authors haven't mentioned any measure and didn't mention any statistical method or tools that can help in analyzing and reporting findings from any MIH study. 3. Whether the authors consider providing such a list of summary measures or not, they should also think of providing a list of key/major/common summary measures found in the papers they considered and find a way to report their finding via meta-analysis approach. Minor point: On page 4, line 43-44: there are several parentheses that, in my opinion, should not be presented here or kept to a strict minimum.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Juliana Feltrin de Souza

Institution and Country: Department of Stomatology, Universidade Federal do paraná, Brazil

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below this systematic review brings a fundamental discussion about the "Outcome and comparator choice" in clinical studies addressing Molar incisor hypomineralization. It is an original idea and valuable for future clinical studies focus on MIH. However, the paper brings a superficial discussion about the MIH and their outcomes and comparator choice. The idea of the "Core Outcome Measurement Instrument Sets" requires a deeper knowledge and discussion about the MIH and their outcomes.

ABSTRACT:

1. Describe "COS" it is the first time that its appear;

Our response: This was done.

2. Describe in the results section the SNA results;

It is not clear the terms "clinically- and patient-centered Outcomes". In my point of view, it appears obvious. If you are evaluating the observational and clinical trials studies about the interventions in MIH, what others outcome could you expect?

Our response: We have expanded on this. However, note that in many studies in dentistry, surrogates (e.g. margin integrities) are used as outcomes; these are neither clinically- nor patient-centered. This was clarified.

STRENGTHS AND LIMITATIONS OF THIS STUDY

States the actual/true "Strengths and limitations of the study" and not repeat the objective of the study.

Our response: This was done.

INTRODUCTION

Page 3 LINE 18: "also, researchers usually collected a range of outcomes, without necessarily reporting all of them later on. This may lead to selective reporting and introduce significant bias." Explain the "and introduce significant bias". Could be the bais of unpublished data?

Our response: Yes, bias due to selective reporting, but also publicatio bias was meant here. This was clarified.

Page 3 Line 15 and 32 the term further stakeholders. Who are the "further stakeholders"? Line 32: Why you use the terms patient and further stakeholders? Are there others further stakeholders besides the patients?

Our response: Further stakeholder such as researchers, regulatory agencies, insurance companies, etc. This was explained.

Page 3 Paragraphs line48/54: Describe the clinical presentations and consequences of the MIH. This information are the fundamental point to justify your study, once it determines the variety of outcome and comparators.

Our response: This was done.

Methods:

It is not clear if the terms "molar incisor hypomineralisation) OR molar incisor hypomineralization) OR mih" could include all studies with MIH. Because this term is after 2001, there are previous studies describing MIH with other terms such as "cheese molars". It could be a limitation of the study.

Our response: Yes, indeed it may be. However, we were interested in studies actually applying the definition MIH. Studies before 2001 may have used definitions which included MIH, but also other conditions, or may have not been precise enough to exactly know if MIH was included at all. We highlighted this.

About the eligible criteria, it is not clear the exclusion aspects, language, studies design. For example, a case report is a design of the observational study, is it included? Is there language restriction?

Our response: This was clarified.

Results:

Page 6 line 16: "A list of comparators was compiled and comparators grouped into agreed categories (Table 2)." The Table 2 describes the outcomes or comparators?

Our response: This was corrected.

Page 6 Line 58: Please correct: "were incl10uded (Fig. 1)"

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According described about the comparators analysis "Statistical analysis included the assessment of the degree (average number of comparators per node) and the clustering coefficient (values of one indicate that all possible connections were made, while values of 0, indicate that only the minimum number of connections were made)". Does it make sense to apply this analysis only in clinical study? Because in observational studies could be not performed comparations.

Our response: We have revised the introduction of single-arm studies; they are not – as they truly are – not connected to any network. Social network statistics were only applied to the main networks in the molar and the incisor group. We highlighted that.

Page 8 line 3 "The cluster coefficient was 0.69, indicating that there were "cliques" of comparators present, with comparators being mainly compared within and not across these cliques. " Is there a cuff-off points of cluster coefficient and its interpretation? What is meaning "cliques"?

Our response: No, there is not. We explain this now.

Page 9 1st paragraph: "The outcomes used in MIH intervention studies focused on two areas; restoration success (measured via the USPHS criteria or similar tools) and pain and hypersensitivity management (measured via scales like the Visual analogue scale or the Schiff Cold Air Sensitivity Scale). Combined, these two areas accounted for 45% of primary outcomes and for 50% of all reported outcomes." It is important discuss about it. Why is important this outcome, what is the differences in MIH? It is a fundamental paragraph of the discussion, about the outcomes. Here, it was required to be involved with the context, MIH, describing the differences of outcome for molars and for incisors. In my opinion, the important outcome for both is the survival of the enamel until its breakdown or caries lesion or survival of the restoration clinically adequate, in other words, the success rate of remineralization or restoration. Please, discuss about this outcome, adding information about the difficulties of MIH managing.

Our response: This was done.

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Our response: We understand your reservation and have accommodated this by separartiing the analyses on molars and incisors. Hence, on molars, the focus will be management of hypersensitivity, caries and breakdown, which are all somewhat related, while on incisors, aesthetics will be the main aspect. We also discuss this aspect now.

Page 11 line 10: "our SNA results implicate that current evidence may not be robust."

Do only your analysis power to state it? Or was it based on all methodological aspects of the primary study?

Our response: This was only based on our SNA results. We explained this in more detail now.

Figure 3: The network graph could be applied for molars and for incisor separately?

Our response: This was done.

Add on the legend the mean of "PMC" and "CPP-ACP"

Our response: This was done.

The terms "infiltration" and "conditioning" were comparators for clinical or observational studies?

Our response: These were only applied for interventional studies, as they are both associated w interventions.

Table 2: About the outcome "mineral gain" it was measured by Laserfluorescence readings Scanning electron microscope (SEM)/ Energy Dispersive X-ray Spectrometry (EDX) Quantitative Light-Induced Fluorescence (QLF) SEM and EDX are applied on in vitro studies. It was performed on this clinical/observational studies?

Our response: Yes, they were performed on the included clinical/observational studies since Baroni and Marchionni (2011) used them in an Ex vivo study collecting samples in vivo and working on them in vitro with the following techniques: Scanning electron microscope (SEM)/ Energy Dispersive X-ray Spectrometry (EDX) Quantitative Light-Induced Fluorescence (QLF)

Reviewer: 2

Reviewer Name: Mihiri Silva

Institution and Country: Inflammatory Origins, Murdoch Children's Research Institute

Please state any competing interests or state 'None declared': None declared

Overall:

This manuscript addresses an important issue in paediatrics and is a robust and well written contribution to the evidence base regarding the management of teeth affected by Molar Incisor Hypomineralisation. It is commended for its clear, rigorous methodology and meaningful discussion. This study is valuable not only for its implications in terms of directing future studies of MIH but also for setting an excellent example of conducting research with a more holistic and patient centered focus. The manuscript does require close editing as there are a number of minor typographical errors.

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"…researchers tend to publish multiple reports from the same clinical trial"

Our response: This was done.

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"However, data is then divided across multiple publications, and linking articles together or with registered protocols can be difficult"

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Our response: This was clarified.

Reviewer: 3

Reviewer Name: Roland Matsouaka

Institution and Country: Duke University, North Carolina, US

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

In this paper, Elhennawy et al., propose to investigate different outcomes and comparators used in molecular incisor hypomineralization (MIH) studies to establish a list of core of the important tools.

Current studies in MIH use a wide range of outcomes and comparators, which make it difficult to know whether these studies:

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Therefore, it is important to develop a core outcome set (COS) for MIH along with current comparators. This paper provide a review of outcomes used in MIH studies to inform such a development of COS. The objective of this study is clear and is of great significance.

There are some major flaws/limitations I would like to point out:

1. Although the disease/condition, subject of this study, is named, there is nowhere in the manuscript where the authors have described the conditions, presented the symptoms/issues related to this conditions, or explained the rationale/driving force that lead investigators to use a wide range of outcomes and comparators for MIH. Although this might be obvious to the authors, this is not the case for all potential readers of the manuscript (including me).

Our response: This was added.

2. The authors didn't provide the list of summary (statistical) measures that were used in the papers they evaluated. Making a recommendation of what outcomes to use should also allow future investigators to know which measures are important for reporting their findings. Providing summary measures is indeed the next to last item on the PRISMA 2009 Checklist. Unfortunately, the authors haven't mentioned any measure and didn't mention any statistical method or tools that can help in analyzing and reporting findings from any MIH study.

Our response: Performing a quantitative synthesis was not in the scope of this paper. This is not a review and meta-analysis, but serves to define COS. No paper with this focus has performed, to our knowledge, a meta-analysis alongside, as measuring effect strengths is not the aim of this research endeavor.

3. Whether the authors consider providing such a list of summary measures or not, they should also think of providing a list of key/major/common summary measures found in the papers they considered and find a way to report their finding via meta-analysis approach.

Our response: Please see our comment above. We further refer to the COMET website and associated papers, which do not recommend meta-analysis as mandatory item during COS definition.

Minor point:

On page 4, line 43-44: there are several parentheses that, in my opinion, should not be presented here or kept to a strict minimum.

Our response: This was done

VERSION 2 – REVIEW

REVIEWER	Roland Matsouaka Duke University, North Carolina, US
REVIEW RETURNED	06-May-2019

GENERAL COMMENTS	The authors have responded thoroughly to the questions asked. They have also updated the manuscript accordingly. I don't have further comments or suggestions.