PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	fiTolerability of statin-based management of patient with history of statin-associated muscle symptoms: protocol for a systematic review
AUTHORS	Villoz, Fanny; Lyko, Christina; Del Giovane, Cinzia; Rodondi, Nicolas; Blum, Manuel

VERSION 1 – REVIEW

REVIEWER	Munkhaugen, John Vestre Viken Hospital Trust
REVIEW RETURNED	07-May-2021

GENERAL COMMENTS	Thank you for this design paper describing a planned systematic review and meta-analysis aiming to summarize the evidence regarding tolerability, acceptability and effectiveness of statin-based therapy management of patients with history of SAMS. The manuscript is well-written, the planned methods are sound and the results will be of importance for daily clinical practice. I have some comments that hopefully will further strengthen your manuscript: - Introduction section, first paragraph: I suggest that you add a brief definition of the SAMS phenomenon. Also, in light of recent RCT evidence, I would suggest using a different term than “common adverse effect” (page 6, line 63) when describing SAMS. Perhaps rather refer to SAMS as commonly reported muscle symptoms in statin treated individuals. - Intro, page 6, line 71: “…intolerance”. You may also define statin intolerance and explain the difference between intolerance and SAMS. - Page 6, lines 60-64. Maybe you could underscore that the prevalence rates (i.e. 5-29%) is based on observational data or registries reported by patients. - Intro, page 6, line 68: “….different strategies..» Do you mean strategies to manage patients with SAMS? - Page 6, line 94, “ in English from inception until August 2020..”. Should you consider to also screen non-English abstracts? You also included the StatinWise Trial published this year, so you should maybe change to August 2021. Indeed, I will recommend you to perform an updated literature search just before submitting the meta-analysis to a journal to ensure that all recent studies are included. - Page 7, line 104 and 105: We will also include studies examining adults previously on statins with a history of statin intolerance without precision of SAMS or other intolerance.” What do you mean when stating “..without precision of SAMS..” Please clarify. - Page 8, lines 145-146: “In line with the Cochrane Handbook for Systematic Reviews of Interventions, “ I suggest that you remove this statement and add a reference to the Cochrane Handbook.

	"..two trained reviewers..». I assume that these are among the authors. The first letter in their first name and family name may be mentioned? - Page 9, line 196: "When dealing with crossover trials, only data before the cross-over will be analyzed". Why will you restrict the analyses to data before crossover? At least three of the trials have a crossover design which both increase power and allow individual differences in muscle complaints to be assessed. I will recommend that you also analyse data after the crossover unless there are very good reasons. If so, these should be carefully explained. - Page 9, lines 202-207: You should specify the difference between SAMS and statin intolerance. I also recommend that you pre-specify analyses according to i. whether they are on a statin or not at study inclusion and ii. study design (RCT vs not, and eventually crossover trial vs. parallel-group design). - You may consider to refer to the planned meta-analysis from the Cholesterol Treatment Trialists' (CTT) Collaboration even though this will be not restricted to patients with SAMS, (Am Heart J. 2016 Jun; 176: 63–69. doi: 10.1016/j.ahj.2016.01.016)

REVIEWER	Carris, Nicholas University of Florida
REVIEW RETURNED	11-May-2021

GENERAL COMMENTS	Thank you for the opportunity to review the article titled, "Tolerability of statin-based management of patient with history of statin-associated muscle symptoms: protocol for a systematic review". I think this is an important topic as CV disease remains the leading cause of death worldwide, up to 20% of patients stop statins due to side effects, and some in the literature touting a nocebo effect offer no practicable solution to the excess deaths from statin intolerance. What's more, while alternative medications are available (e.g., PCSK9 inhibitors, bempedoic acid) their use may be limited by cost, route of administration, or lack of outcome data. As such, this is certainly and important topic worthy of detailed exploration. Overall, the paper is very well written and the plan is well thought out. Point by point comments below. - Major Comments - Should adjust dates to include N-of-1 trials published in BMJ and NEJM. Page 4 (page 7 of pdf) line 93 says "non-randomized studies with control group", in the abstract it says, "non-randomized trials with a control group". To me these are different things. I would be explicit and consistent. - Minor comments / suggestions - Would this protocol include post-hoc analysis of prior randomized controlled trial so long as there was a comparison group? Would this protocol include cohort studies (prospective or retrospective) provided there is a control group? What is the rationale for excluding studies which seek to improve statin tolerability in statin naïve patients? Page 7 (PDF page 10) line 187, this is an assumption I'm sure the authors are not terribly fond of, and neither am I. There is no better alternative I can think of, however, with all the other plans to contact authors for incomplete data, might I suggest add this point as well, that being, to request the number of patients with > 0 events. I like the search strategy through number 7. After number 7 it appears the authors are attempting to narrow search results (and rightly so). However, they seem to be

	attempting to draw out specific parts of trials which will be reported to better identify the types of studies to include. However, my concern is perhaps these details may not be reported in the proper place and the search seems to be targeting title, abstract, and key words. Additionally, #12 does not include the word “trial” as a term to itself. Overall, my concern is the search being slightly on the restrictive side and counting on backward and forward citation search to ensure catching all pertinent articles. I wonder if it would be a cleaner search to exclude what you do not want (e.g., reviews, commentary, etc.). Date criteria aside, I don’t think the search would catch this important citation (https://pubmed.ncbi.nlm.nih.gov/33196154/) I don’t even think with backward and forward citation review it would be caught, the closest article would be this one (which still might not be included - https://www.sciencedirect.com/science/article/pii/S0021915021001210?via%3Dihub)

VERSION 1 – AUTHOR RESPONSE

Reviewer Reports:
Reviewer: 1 Dr. John Munkhaugen, Vestre Viken Hospital Trust
Thank you for this design paper describing a planned systematic review and meta-analysis aiming to summarize the evidence regarding tolerability, acceptability and effectiveness of statin-based therapy management of patients with history of SAMS. The manuscript is well-written, the planned methods are sound and the results will be of importance for daily clinical practice. I have some comments that hopefully will further strengthen your manuscript:
Our answer: Thank you for your appreciation.

2. Introduction section, first paragraph: I suggest that you add a brief definition of the SAMS phenomenon. Also, in light of recent RCT evidence, I would suggest using a different term than “common adverse effect” (page 6, line 63) when describing SAMS. Perhaps rather refer to SAMS as commonly reported muscle symptoms in statin treated individuals.
Our answer: Thank you for your recommendation. We have added a brief definition of the SAMS phenomenon and we have replaced ¨common adverse effect¨ with ¨commonly reported muscle symptoms¨ as suggested.
Page 4, line 62-63 : ¨Statin-associated muscle symptoms (SAMS), a composite of muscle symptoms appearing consequent to the initiation or the increase of a statin’s treatment [1], […].¨
Page 4, line 67: ¨Nevertheless, SAMS, a commonly reported muscle symptom threatens the ability of a significant proportion of patients to tolerate evidence-based dosing: […].¨

3. Intro, page 6, line 71: “…intolerance”. You may also define statin intolerance and explain the difference between intolerance and SAMS.
Our answer: We have updated the description of statin intolerance and the difference between statin intolerance and SAMS in the types of participants’ paragraph in the method’s section. In order to avoid confusion in the introduction paragraph, we have decided to mention only SAMS instead of intolerance in this sentence.
Page 4, line 78: ¨ […] without previous SAMS in 2017 […]. ¨
Page 5, line 171-175: ¨Indeed, SAMS is a type of statin intolerance concerning specifically muscle symptoms. Nevertheless, some participants can also report other types of intolerance, as for example, impaired cognition [18], hepatic dysfunction [19] or depression [20]. SAMS is also a recent definition and could have been reported as “intolerance” or “muscle related adverse events” in the past.¨

4. Page 6, lines 60-64. Maybe you could underscore that the prevalence rates (i.e. 5-29%) is based on observational data or registries reported by patients.

Our answer: Thank you for this suggestion. We have underscored the prevalence rates with the explicit mention of the source as observational data or registries reported by patients.
Page 4, line 68-70: ¨[…]:based on observational data or registries reported by patients, SAMS affects between 5-29% of statin treated individuals.¨

5. Intro, page 6, line 68: "….different strategies..» Do you mean strategies to manage patients with SAMS?
Our answer: Thank for this comment. We have added precision as requested.
Page 4, line 74-76: ¨ European Atherosclerosis Society Consensus Panel Statement recommend multiple different strategies to manage patients with SAMS but they are based only on experts' opinion due to lack of sufficient data.¨

6. Page 6, line 94, " in English from inception until August 2020..". Should you consider to also screen non-English abstracts? You also included the StatinWise Trial published this year, so you should maybe change to August 2021. Indeed, I will recommend you to perform an updated literature search just before submitting the meta-analysis to a journal to ensure that all recent studies are included.
Our answer: Thank you for pointing out this limitation. We have decided to exclude non-English abstracts due to the lack of language resources and the possibly low impact of these abstracts on conclusion.[1] English is nowadays a universal language in scientific fields and the language bias may have been decreasing. Moreover, the use of the English language can be an indicator of higher methodological quality. [2]
See Editor's comment #1 on updated search.

7. Page 7, line 104 and 105: We will also include studies examining adults previously on statins with a history of statin intolerance without precision of SAMS or other intolerance." What do you mean when stating "..without precision of SAMS.." Please clarify.
Our answer: See 1st Reviewer's comment #3.

8. Page 8, lines 145-146: "In line with the Cochrane Handbook for Systematic Reviews of Interventions, " I suggest that you remove this statement and add a reference to the Cochrane Handbook. "..two trained reviewers..». I assume that these are among the authors. The first letter in their first name and family name may be mentioned?
Our answer: "Thank you for your recommendation. We have updated the text as follows:
Page 6, line 216: ¨ Two trained reviewers (VF and LC) will evaluate independently eligibility based on titles and abstracts of all studies retrieved in our electronic search. [21]¨

9. Page 9, line 196: "When dealing with crossover trials, only data before the cross-over will be analyzed". Why will you restrict the analyses to data before crossover? At least three of the trials have a crossover design which both increase power and allow individual differences in muscle complaints to be assessed. I will recommend that you also analyse data after the crossover unless there are very good reasons. If so, these should be carefully explained.
Our answer: Thank you for pointing out this limitation. We agree and we have removed this restriction as follow:
Page 7, line 275-276: ¨ When dealing with crossover trials, data after the crossover will be analyzed.¨

10. Page 9, lines 202-207: You should specify the difference between SAMS and statin intolerance. I also recommend that you pre-specify analyses according to i. whether they are on a statin or not at study inclusion and ii. study design (RCT vs not, and eventually crossover trial vs. parallel-group design).
Our answer: See 1st Reviewer's comment #3.
Thank you for your recommendation. We have added a pre-specified analysis according to whether participants are on a statin or not at study inclusion.

Page 7, line 286: ¨pre-planned variables to explore are primary versus secondary prevention, high intensity versus non-high intensity statins, intermittent dosing versus daily dosing, patients with a history of SAMS versus patients with a history of statin intolerance, only statin interventions versus statin and additional interventions and participants with versus without a statin at inclusion.¨
We already planned to do subgroups analysis depending on study design: Page 7, line 219-220. ¨ Regarding the variety of study designs, we will first pool data, then analyze data from different type of studies separately.¨ We rephrased it to make it more explicit:
Page 7, line 273-275: ¨Regarding the variety of study designs, we will first pool data, then analyze data from different type of studies separately (E.g. RCT versus non randomized control studies, crossover trial versus parallel trial).¨

11. You may consider to refer to the planned meta-analysis from the Cholesterol Treatment Trialists' (CTT) Collaboration even though this will be not restricted to patients with SAMS, (Am Heart J. 2016 Jun; 176: 63–69. doi: 10.1016/j.ahj.2016.01.016)
Our answer: Thank you for this suggestion. We have added a reference from the planned meta-analysis from the Cholesterol Treatment Trialists' (CTT) Collaboration.
Page 4, line 93-95: ¨Our systematic review and meta-analysis will be complementary to the ongoing meta-analysis [17] on statin adverse events with the particularity to focus on patients with a history of SAMS and SAMS' management.¨

Reviewer: 2 Dr. Nicholas Carris, University of Florida
Thank you for the opportunity to review the article titled, "Tolerability of statin-based management of patient with history of statin-associated muscle symptoms: protocol for a systematic review". I think this is an important topic as CV disease remains the leading cause of death worldwide, up to 20% of patients stop statins due to side effects, and some in the literature touting a nocebo effect offer no practicable solution to the excess deaths from statin intolerance. What's more, while alternative medications are available (e.g., PCSK9 inhibitors, bempedoic acid) their use may be limited by cost, route of administration, or lack of outcome data. As such, this is certainly and important topic worthy of detailed exploration. Overall, the paper is very well written and the plan is well thought out. Point by point comments below.
Our answer: Thank you for your appreciation.

- Major Comments -
12. Should adjust dates to include N-of-1 trials published in BMJ and NEJM.
Our answer: see Editor's comment #1 on updated search.

13. Page 4 (page 7 of pdf) line 93 says "non-randomized studies with control group", in the abstract it says, "non-randomized trials with a control group". To me these are different things. I would be explicit and consistent.
Our answer: Thank you for pointing out this inconsistency. We modified ¨trials¨ to ¨studies¨ in the abstract, line 29.

Minor comments / suggestions -
14. Would this protocol include post-hoc analysis of prior randomized controlled trial so long as there was a comparison group?
Our answer: Indeed, we will not exclude post-hoc analysis of prior randomized controlled trial so long as there was a comparison group. We have updated the text as follows:
Page 6, line 225-226: "We will include post-hoc analysis of prior randomized controlled trial so long as there is a comparison group."

15. Would this protocol include cohort studies (prospective or retrospective) provided there is a control group?

Our answer: Yes, it was what we had meant with “non-randomized studies with control group”. We have updated the description as follows:
Page 4, line 102-103: “We will include human randomized controlled trials and prospective and retrospective cohort studies with a control group, published in English from inception until April 2021.”

16. What is the rationale for excluding studies which seek to improve statin tolerability in statin naïve patients?
Our answer: Thank you for your comment. The rationale is that we want to address the practical question of the management of patients with a history of SAMS, as guidelines recommend multiple different strategies to manage patients with SAMS but are based only on experts’ opinion due to lack of systematic appraisal of the available data.[3]

17. Page 7 (PDF page 10) line 187, this is an assumption I’m sure the authors are not terribly fond of, and neither am I. There is no better alternative I can think of, however, with all the other plans to contact authors for incomplete data, might I suggest add this point as well, that being, to request the number of patients with > 0 events.
Our answer: Thank you for your recommendation. We will also contact authors to request the number of patients with > 0 events. We modified the paragraph as requested.
Page 7, line 264-267: “When studies reported the number of muscle events instead of the number of subjects experiencing muscular event, we will contact the authors to request the number of patients with > 0 events. If this could not be addressed, we will make the assumption of one event per subject.”

18. I like the search strategy through number 7. After number 7 it appears the authors are attempting to narrow search results (and rightly so). However, they seem to be attempting to draw out specific parts of trials which will be reported to better identify the types of studies to include. However, my concern is perhaps these details may not be reported in the proper place and the search seems to be targeting title, abstract, and key words. Additionally, #12 does not include the word “trial” as a term to itself. Overall, my concern is the search being slightly on the restrictive side and counting on backward and forward citation search to ensure catching all pertinent articles. I wonder if it would be a cleaner search to exclude what you do not want (e.g., reviews, commentary, etc.). Date criteria aside, I don’t think the search would catch this important citation (https://pubmed.ncbi.nlm.nih.gov/33196154/) I don’t even think with backward and forward citation review it would be caught, the closest article would be this one (which still might not be included - https://www.sciencedirect.com/science/article/pii/S0021915021001210?via%3Dihub)
Our answer: Thank you for your concern. We have developed the search strategy in collaboration with a trained librarian. Concerning #12, Cochrane RCT Filter adapted for Embase.com filter was created by free text terms and Emtree terms stated in the Cochrane Handbook Section 6.3.2.2 (Version 5).[4] Concerning this important citation (https://pubmed.ncbi.nlm.nih.gov/33196154), we have already included it with its ClinicalTrials.gov record in our search in August 2020. (London, I.C., Self-Assessment Method for Statin Side-effects Or Nocebo. 2016, https://ClinicalTrials.gov/show/NCT02668016). Moreover, we ran the search again in April 2021. At this time, we have caught the record of Herrett et al, 2021 [5] , which cites the citation of interest [6] in their reference. Therefore, we found it also in our backward and forward citation review. This article does not have any abstract and is a correspondence letter making it difficult to be caught by any search strategy. For these reasons, we prefer not change our strategy.

Reference
1. Nussbaumer-Streit, B., et al., Excluding non-English publications from evidence-syntheses did not change conclusions: a meta-epidemiological study. J Clin Epidemiol, 2020. 118: p. 42-54.
2. Jüni, P., et al., Direction and impact of language bias in meta-analyses of controlled trials: empirical study. Int J Epidemiol, 2002. 31(1): p. 115-23.

3. Stroes, E.S., et al., Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J, 2015. 36(17): p. 1012-22.
4. Lefebvre, C., et al., Searching for and selecting studies, in Cochrane Handbook for Systematic Reviews of Interventions. 2019. p. 67-107.
5. Herrett, E., et al., Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials. BMJ, 2021. 372: p. n135.
6. Wood, F.A., et al., N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects. N Engl J Med, 2020. 383(22): p. 2182-2184.

VERSION 2 – REVIEW

REVIEWER	Munkhaugen, John Vestre Viken Hospital Trust
REVIEW RETURNED	16-Jun-2021

GENERAL COMMENTS	Thank you very much for responding to all my concerns. I have no further comments. I look forward to the results!