ARTICLE DETAILS

TITLE (PROVISIONAL)	Functional lesional neurosurgery for tremor – a protocol for a systematic review and meta-analysis
AUTHORS	Schreglmann, Sebastian; Krauss, Joachim; Chang, Jin Woo; Bhatia, Kailash; Kaegi, Georg

VERSION 1 - REVIEW

REVIEWER	Alfonso Fasano Associate Professor - University of Toronto, Canada Krembil Research Institute, Toronto, Ontario, Canada Movement Disorders Centre - Toronto Western Hospital, Toronto, Ontario, Canada
REVIEW RETURNED	23-Dec-2016

GENERAL COMMENTS	Authors describe a novel procedure on how to review the existing literature on efficacy and persistent side effects of lesional neurosurgical treatment for tremor due to Parkinson`s disease, Essential Tremor, Multiple Sclerosis and midbrain / rubral tremor. Text and methods are clear, I do not see a real reason to include only papers with more than 5 patients, and even if so, why 5? Although less important, the same would apply to the cut-off of 2 months after the intervention

REVIEWER	Federico Micheli University of Buenos Aires
REVIEW RETURNED	29-Dec-2016

GENERAL COMMENTS	It is an interesting proposal but the grammar has to be improved by a native English speaker, before it can be accepted

REVIEWER	Yoshinori Higuchi Department of Neurological Surgery, Chiba University Graduate School of Medicine, Japan
REVIEW RETURNED	06-Feb-2017

GENERAL COMMENTS	The authors demonstrated a protocol of systematic review of ablation surgery for intractable tremor. The number of prospective studies is very limited in this field. I agree that heterogeneity in study design complicate the interpretation. Various tremor rating scales made it difficult to summarize the outcomes. The authors will use standardized mean difference (Hedge`s g) and resolve this problem. I have a few comments.

	1. Adverse effects from lesional surgery is crucial for comparison of treatment options. However, the authors also need to evaluate recurrence of symptom. 2. The data should be collected from reports using MRI-based treatment planning. Ventriculography or CT-based treatment planning is not suitable for comparison of present treatment efficacy.

REVIEWER	Al Fenoy University of Texas Houston Health Science Center USA
REVIEW RETURNED	14-Feb-2017

GENERAL COMMENTS	Very nice study protocol. We need to have a meta-analysis performed of lesional procedures for tremor to see true efficacy, longevity of effect, and side effect profile as compared to stimulation. It will be nice to see the finished product. 1. How will you compare effect for the (smaller) studies with follow-up times that are earlier or later than the timepoint chosen that retains the most in the analysis, as described in lines 163-164? Will those studies just be excluded, or will those patients/effects be placed in another category? 2. Comaring PD tremor with other tremor, the scales used are likely different using UPDRS III vs. other scales. Mean improvement is good to combine all tremor, but if after preliminary analysis the articles all relating PD tremor improvement use the UPDRS III, should not that be used as well? 3. Small English grammar/spelling corrections Line 102 losing instead of loosing Line 105 its instead of it's Line 163 choose instead of chose

REVIEWER	Jeff Bronstein David Geffen School of Medicine at UCLA USA
REVIEW RETURNED	14-Feb-2017

GENERAL COMMENTS	This is a Protocol manuscript describing a systematic review and meta-analysis of the literature on neurosurgical lesions for the treatment of tremor. The manuscript is well-written and the proposed protocol meets the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015. The authors are expert in the field and I look forward to the results of such a review.

REVIEWER	Ron L. Alterman, MD Beth Israel Deaconess Medical Center Harvard Medical School
REVIEW RETURNED	18-Feb-2017

GENERAL COMMENTS	In this manuscript the authors present their plan for performing a detailed meta-analysis of central ablative procedures for the treatment of tremor. Their research plan is sound, they have defined a reasonable primary outcome measure and useful secondary measures of safety and efficacay. They are honest in their

	discussion of the potential pit-falls and limitations of their approach. My only substantive disagreement with the authors concerns the utility of the results their endeavors will yield. While it will be useful to have the cumulative experience of lesioning for tremor in one paper, the results will not address the key questions regarding the best surgical intervention for treating tremor in the early 21st century. Those, like myself, who favor deep brain stimulation to ablation will point to the direct comparisons of thalamic DBS to thalamotomy, which will be excluded from this analysis, and state correctly that DBS remains the safer and equally efficacious option. On the other hand, those who favor MRgFUS will state that the results of this study do not reflect those achievable with this novel "non-invasive" technology and therefore do not apply. Finally, as there are very few long-term studies of thalamotomy cohorts, this study will add little to our knowledge in this regard.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Alfonso Fasano
Institution and Country: Associate Professor - University of Toronto, Canada; Krembil Research Institute, Toronto, Ontario, Canada; Movement Disorders Centre - Toronto Western Hospital, Toronto, Ontario, Canada Please state any competing interests or state 'None declared': None
Authors describe a novel procedure on how to review the existing literature on efficacy and persistent side effects of lesional neurosurgical treatment for tremor due to Parkinson`s disease, Essential Tremor, Multiple Sclerosis and midbrain / rubral tremor. Text and methods are clear, I do not see a real reason to include only papers with more than 5 patients, and even if so, why 5? Although less important, the same would apply to the cut-off of 2 months after the intervention.

We thank Prof. Fasano for his positive judgement of our protocol. We think that at least an n=5 and follow-up of 2 months per cohort should be provided in order to guarantee a minimum consistency of procedures and cohorts. Similar to the other in-/exclusion criteria chosen this was decided in order to minimize reporting bias, which is particularly frequent in smaller cohorts and case reports and with less consistent follow-up.

Reviewer: 2
Reviewer Name: Federico Micheli
Institution and Country: University of Buenos Aires Please state any competing interests or state 'None declared': None declared
It is an interesting proposal but the grammar has to be improved by a native English speaker, before it can be accepted.

We thank Prof. Micheli that he judges our protocol favourably. Prof. KP Bhatia, one of the authors of this work has been living and working in London/UK for over 30 years and we would like to leave it to the discretion of the editorial office to judge if additional language checks should be implemented.

Reviewer: 3
Reviewer Name: Yoshinori Higuchi
Institution and Country: Department of Neurological Surgery, Chiba University Graduate School of Medicine, Japan Please state any competing interests or state 'None declared': None decleared
Authors demonstrated a protocol of systematic review of ablation surgery for intractable tremor. The number of prospective studies is very limited in this field. I agree that heterogeneity in study design

complicate the interpretation. Various tremor rating scales made it difficult to summarize the outcomes. The authors will use standardized mean difference (Hedge`s g) and resolve this problem. I have a few comments.

1. Adverse effects from lesional surgery is crucial for comparison of treatment options. However, the authors also need to evaluate recurrence of symptom.

2. The data should be collected from reports using MRI-based treatment planning. Ventriculography or CT-based treatment planning is not suitable for comparison of present treatment efficacy.

We thank Prof. Higuchi for his comments. Ideally this study should be able to address the topic of recurrence of symptoms / tremor. However, as far as we have assessed the literature by now, the mentioned paucity of prospective studies as well as the inhomogeneous follow-up rates between studies preclude a reasonable assessment of tremor recurrence. We will however address this issue in the narrative part of the discussion and have included a sentence in line 240-241.

With regards to the targeting modality used we did not plan to restrict the review to a particular modality, as this would lead to further fragmentation of results, although we agree that ventriculography and CT-based planning is not used anymore at least in the western hemisphere academic setting – we have added the latter in line 235-237.

Reviewer: 4
Reviewer Name: Al Fenoy
Institution and Country: University of Texas Houston Health Science Center, USA Please state any competing interests or state 'None declared': none declared

Very nice study protocol. We need to have a meta-analysis performed of lesional procedures for tremor to see true efficacy, longevity of effect, and side effect profile as compared to stimulation. It will be nice to see the finished product.

1. How will you compare effect for the (smaller) studies with follow-up times that are earlier or later than the timepoint chosen that retains the most in the analysis, as described in lines 163-164? Will those studies just be excluded, or will those patients/effects be placed in another category?

2. Comaring PD tremor with other tremor, the scales used are likely different using UPDRS III vs. other scales. Mean improvement is good to combine all tremor, but if after preliminary analysis the articles all relating PD tremor improvement use the UPDRS III, should not that be used as well?

3. Small English grammar/spelling corrections Line 102 losing instead of loosing Line 105 its instead of it's Line 163 choose instead of chose

We thank Prof. Fenoy for his positive feedback and relevant remarks. Ad 1: We are planning to use the follow-up time point that retains the largest number of patients per cohort, as described in lines 205-206, i.e. if after baseline (n=20) results at 3 months are given for n=18 and at 12 months for n=14 we will choose the mean tremor reduction until 3 months. The data of the other follow-up time-points will not be included in the meta-analysis but may be included in the narrative discussion of results.

Ad 2: From our first assessments of the literature it has become clear that even the PD studies that used the UPDRS scale for quantification by no means all reported the same items for tremor, again making a direct comparison very difficult. Furthermore, we think reporting the efficacy on tremor from different aetiologies is easier to compare using the same measure. We therefore have only planned to use the standardized mean difference (Hedge`s g) for comparison.

Ad 3: We have corrected the typos highlighted.

Reviewer: 5
Reviewer Name: Jeff Bronstein
Institution and Country: David Geffen School of Medicine at UCLA, USA Please state any competing interests or state 'None declared': None declared

This is a Protocol manuscript describing a systematic review and meta-analysis of the literature on neurosurgical lesions for the treatment of tremor. The manuscript is well-written and the proposed protocol meets the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015. The authors are expert in the field and I look forward to the results of such a review.

We thank Prof. Bronstein for his very encouraging verdict.

Reviewer: 6
Reviewer Name: Ron L. Alterman, MD
Institution and Country: Beth Israel Deaconess Medical Center, Harvard Medical School Please state any competing interests or state 'None declared': I have no competing interests
In this manuscript the authors present their plan for performing a detailed meta-analysis of central ablative procedures for the treatment of tremor. Their research plan is sound, they have defined a reasonable primary outcome measure and useful secondary measures of safety and efficacay. They are honest in their discussion of the potential pit-falls and limitations of their approach. My only substantive disagreement with the authors concerns the utility of the results their endeavors will yield. While it will be useful to have the cumulative experience of lesioning for tremor in one paper, the results will not address the key questions regarding the best surgical intervention for treating tremor in the early 21st century. Those, like myself, who favor deep brain stimulation to ablation will point to the direct comparisons of thalamic DBS to thalamotomy, which will be excluded from this analysis, and state correctly that DBS remains the safer and equally efficacious option. On the other hand, those who favor MRgFUS will state that the results of this study do not reflect those achievable with this novel "non-invasive" technology and therefore do not apply. Finally, as there are very few long-term studies of thalamotomy cohorts, this study will add little to our knowledge in this regard.

We are grateful for Prof. Alterman`s positive remarks to the quality of our research protocol and the usefulness of a systematic and cumulative assessment of lesional approaches to tremor. We agree that our proposed protocol will not be able to answer the question if DBS or MRIgFUS are superior to treat tremor in the 21st century. Ultimately, more prospective head-to-head comparison studies like the mentioned single study comparing DBS and thalamotomy are needed to answer this question. On the other hand we disagree that this meta-analysis will not contribute to a realistic assessment of the advantages and disadvantages of MRIgFUS treatments, as it will for the first time make the data of different lesional techniques and targets - including incision-less MRIgFUS and Gamma Knife – comparable by a) a systematic assessment, b) recalculating efficacy into a unifying measure using Hedge`s g and c) calculating mean side effect incidence rates.
In addition to that, this first systematic review of the field of lesional tremor treatment will highlight systematic weaknesses of existing data sets with regards to study design, follow-up and consistency.

We also updated the end of our literature review to February 2017 in line 217.

VERSION 2 – REVIEW

REVIEWER	Alfonso Fasano Morton and Gloria Shulman Movement Disorders Centre and the Edmond J. Safra Program in Parkinson's Disease, Toronto Western Hospital, UHN, Division of Neurology, University of Toronto, Toronto, Ontario, Canada
REVIEW RETURNED	25-Mar-2017

GENERAL COMMENTS	I'm satisfied with Authors' reply

REVIEWER	Al Fenoy UT Houston USA
REVIEW RETURNED	27-Mar-2017

GENERAL COMMENTS	previous comments addressed