

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Dexmedetomidine for the prevention of postoperative delirium in patients after intracranial operation for brain tumours (DEPOD study): a study protocol and statistical plan for a multicentre randomised controlled trial
<b>AUTHORS</b>	He, Xuan; Cheng, Kun-Ming; Zhang, Linlin; Gu, Hongqiu; Qu, Xin; Xu, Yuan; Ma, Penglin; Zhou, Jian-Xin

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Balachundhar Subramaniam Beth Israel Deaconess Medical Center A Harvard teaching hospital, Boston, MA, USA.
<b>REVIEW RETURNED</b>	07-Jul-2020

<b>GENERAL COMMENTS</b>	1. CAM ICU even for extubated patients? Why not full CAM? 2. 50% reduction is overzealous? A 33% reduction is a better approach?
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<b>REVIEWER</b>	Adomas Bunevicius Lithuanian University of Health Sciences, Kaunas, Lithuania
<b>REVIEW RETURNED</b>	09-Aug-2020

<b>GENERAL COMMENTS</b>	<p>This is an important and needed study to address the potential efficacy and safety of medical intervention (dexmedetomidine) for prevention of postoperative delirium in patients undergoing surgery for brain tumors. The study is well planned and the manuscript is well written.</p> <p>It appears that authors attempt to include patients with different brain tumors in terms of tumor histological type, infiltration (intraaxial vs. extraxial) and tumor location. It would be interesting to know if there are any plans to stratify tumors by the above-mentioned characteristics.</p> <p>A detailed chart presenting variables that will be collected during the course of the study at different time points is advisable. Will authors evaluate patient education level, which has been shown to predict the incidence of POD after brain tumor surgery?</p> <p>Pre-operative cognitive impairment is often considered an important predictor of elevated risk of postoperative delirium. Unfortunately, but cognitive impairment and mental disorders are often underrecognized in patients with brain tumors. Hence, lack of prospective cognitive assessment can be considered a limitation.</p>
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## VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Balachundhar Subramaniam

Institution and Country:

Beth Israel Deaconess Medical Center

A Harvard teaching hospital, Boston, MA, USA.

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

Please leave your comments for the authors below

1. CAM ICU even for extubated patients? Why not full CAM?

Response: Thank you very much for your comments. During the design of the project, we discussed the selection of a delirium assessment tool and finally decided to use the CAM-ICU mainly due to the following three reasons. First, we performed our study in ICUs. As mentioned in the Participants section (Page 8), our inclusion criteria are “adult patients after elective intracranial operation for brain tumours under general anaesthesia and who are admitted to the ICU directly from the operating room or postoperative care unit”. Thus at least the first delirium will be evaluated at the ICU on the morning of postoperative day one. Second, about a quarter of our patients are endotracheal intubated. In our previous cohort study with 800 neurosurgical patients admitted to the ICU after intracranial operations, 28% of the patients remained endotracheal intubation (PMID 31464712, ref #8). Therefore, we selected the CAM-ICU to maintain consistency for the assessment of delirium during the postoperative day one to five. Third, as one of the most widely recognized delirium screening scale in the ICU, CAM-ICU is recommended by the American Society of Critical Care Medicine in adult ICU patients (PMID 30113379, ref #27) and is suggested by the European Society of Anaesthesiology in postoperative patients (PMID 28187050, ref #1). Additionally, in many cohort studies and controlled studies, CAM-ICU has been employed as an effective delirium assessment tool for the postoperative patients admitted to ICU (for example: PMID 30406871, ref #10; PMID 27542303, ref #17).

We revised the second paragraph in the Summary section to explain the reasons for selecting the CAM-ICU for postoperative delirium assessment. Please see page 20.

2. 50% reduction is overzealous? A 33% reduction is a better approach?

Response: Thank you for your suggestion. We revised the sample size justification as “We assume that the incidence of POD would be reduced by one-third in the dexmedetomidine group compared with the placebo group in the present study”. Taking into account about 5% of the loss to follow-up rate, we corrected the final sample size as 1140 (570 in each group) patients. Please see page 17-18. We have obtained the approval for this change in the protocol by the IRB.

Reviewer: 2

Reviewer Name: Adomas Bunevicius

Institution and Country: Lithuanian University of Health Sciences, Kaunas, Lithuania

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

Please leave your comments for the authors below

This is an important and needed study to address the potential efficacy and safety of medical intervention (dexmedetomidine) for prevention of postoperative delirium in patients undergoing surgery for brain tumors. The study is well planned and the manuscript is well written.

Response: Thank you very much for your review of our manuscript.

It appears that authors attempt to include patients with different brain tumors in terms of tumor histological type, infiltration (intraaxial vs. extraxial) and tumor location. It would be interesting to know if there are any plans to stratify tumors by the above-mentioned characteristics.

Response: Thank you very much for your comments. Yes, tumor histological type and location might be important factors relating to the occurrence of postoperative delirium. In the design of the project, we did not plan the randomization by stratifying the tumor characteristics because the stratification may result in a too-large sample size to be finished in a rational period. However, according to your suggestion, we added a post-hoc analysis by stratifying the patients with tumors as “intra-axial vs. extra-axial”, “supratentorial vs. infratentorial”, and “frontal vs. non-frontal approach craniotomy”. Please see page 18.

A detailed chart presenting variables that will be collected during the course of the study at different time points is advisable. Will authors evaluate patient education level, which has been shown to predict the incidence of POD after brain tumor surgery?

Response: Thank you. We added a table to demonstrate data collection at each time point (please see new Table 1, page 31-32). We will collect the education level in the present study.

Pre-operative cognitive impairment is often considered an important predictor of elevated risk of postoperative delirium. Unfortunately, but cognitive impairment and mental disorders are often underrecognized in patients with brain tumors. Hence, lack of prospective cognitive assessment can be considered a limitation.

Response: Yes, we agree. Although we exclude patients with medical records documented preoperative history of mental or cognitive disorders, no more systematic cognitive assessment will be performed before the intracranial operation. We added this as one limitation in the “Main strengths and limitations of the study” section and the “Summary” section. Please see page 5 and 21.

#### **VERSION 2 – REVIEW**

<b>REVIEWER</b>	Balachundhar Subramaniam Beth Israel Deaconess Medical Center, Boston, MA. 02215
<b>REVIEW RETURNED</b>	19-Oct-2020
<b>GENERAL COMMENTS</b>	The authors have addressed my concerns