PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Optic nerve sheath diameter sonography for the diagnosis of increased intracranial pressure: a systematic review and meta-analysis protocol
AUTHORS	Koziarz, Alex; Sne, Niv; Kegel, Fraser; Alhazzani, Waleed; Nath, Siddharth; Badhiwala, Jetan; Rice, Timothy; Engels, Paul; Samir, Faidi; Healey, Andrew; Kahnamoui, Kamyar; Banfield, Laura; Sharma, Sunjay; Reddy, Kesava; Hawryluk, Gregory; Kirkpatrick, Andrew; Almenawer, Saleh

VERSION 1 - REVIEW

REVIEWER	Donald Duck I am not employed
REVIEW RETURNED	12-Feb-2017

GENERAL COMMENTS	Authors submit paper without results. They should wait until study is completed, and publish it with results in one go.

REVIEWER	Llewellyn Padayachy University of Cape Town South Africa
REVIEW RETURNED	16-Mar-2017

GENERAL COMMENTS	Review of manuscript: Optic nerve sheath diameter sonography for the diagnosis of increased intracranial pressure: a systematic review and meta-analysis protocol. Manuscript ID: bmjopen-2017-016194 This systematic review and meta-analysis protocol has been very well designed. It addresses the very relevant issue of non-invasive assessment of intracranial pressure (ICP), using ultrasound-based measurement of the ONSD. In further planning and execution of this study the following minor points should be considered: The relationship between ICP and ONSD measurement has been described quite widely, however, the cut off value for ONSD measurement that best predicts raised ICP remains a contentious issue. Perhaps the most useful outcome of a review paper of this nature would be to provide some clarity on this issue. A number of reasons exist for this disparity. Various reference standards have been used as surrogate markers for raised ICP.

	As noted in the protocol, imaging features, clinical findings, invasive ICP measurement and lumbar puncture CSF measurement have all been described. It is therefore not really surprising that different ONSD cut off values have been reported. This is further complicated by heterogeneity regarding the threshold for defining raised ICP, as well as the unit of measurement, i.e. mmHg vs. cmH20. A more commonly accepted treatment threshold for raised ICP, i.e. > 20 mmHg should also be considered, as described in the Brain Trauma Foundation guidelines. Age related cut off values are also quite contentious and varied. This needs to be accounted for when reviewing this diagnostic parameter. Certain studies performed in Asia also demonstrate remarkably different ONSD reference and cut off values. Demographic variations therefore also need to be taken into account. It certainly appears as though the elastic, dynamic and hysteresis properties of the ONS have a significant role to play in determining the individual and pathology (acute vs. chronic) related variation in ONSD measurement. Studies describing these features may also be worth including in the review. I look forward to reading the results of this study and hope it will contribute to our understanding of this promising non-invasive marker of ICP.

VERSION 1 – AUTHOR RESPONSE

Responses to reviewers
Reviewer #2:
This systematic review and meta-analysis protocol has been very well designed.
It addresses the very relevant issue of non-invasive assessment of intracranial pressure (ICP), using ultrasound-based measurement of the ONSD.
**Thank you for your thoughtful comments.

In further planning and execution of this study the following minor points should be considered: The relationship between ICP and ONSD measurement has been described quite widely, however, the cut off value for ONSD measurement that best predicts raised ICP remains a contentious issue. Perhaps the most useful outcome of a review paper of this nature would be to provide some clarity on this issue.
**Thank you. We have included in our revised manuscript that we will evaluate our summary cutoff values for ONSD to determine if they are accurate predictors of raised ICP.

A number of reasons exist for this disparity. Various reference standards have been used as surrogate markers for raised ICP. As noted in the protocol, imaging features, clinical findings, invasive ICP measurement and lumbar puncture CSF measurement have all been described. It is therefore not really surprising that different ONSD cut off values have been reported.
**Thank you. We agree with your comment and have included all appropriate reference standards for evaluating the diagnostic accuracy of ONSD measurement for raised ICP.

This is further complicated by heterogeneity regarding the threshold for defining raised ICP, as well as the unit of measurement, i.e. mmHg vs. cmH20. A more commonly accepted treatment threshold for raised ICP, i.e. > 20 mmHg should also be considered, as described in the Brain Trauma Foundation guidelines.
**Thank you. We adopted the most recent cutoff as published in the recent Brain Trauma Foundation (carney et al) guidelines, which indicates that >22 mm Hg warrants treatment because values above

this level are associated with increased mortality. We will also include individual included study's reporting method of high ICP (mm Hg or cm H2O).

Age related cut off values are also quite contentious and varied. This needs to be accounted for when reviewing this diagnostic parameter.
**Thank you. We accounted in the revised manuscript the ages of patients recruited.

Certain studies performed in Asia also demonstrate remarkably different ONSD reference and cut off values. Demographic variations therefore also need to be taken into account.
**Thank you. We have included in our revised manuscript the country of patient recruitment to take demographic variations into account.

It certainly appears as though the elastic, dynamic and hysteresis properties of the ONS have a significant role to play in determining the individual and pathology (acute vs. chronic) related variation in ONSD measurement. Studies describing these features may also be worth including in the review.
**Thank you. We will consider including these studies in our review to better understand the elastic, dynamic and hysteresis properties of the ONS in relation to individual and pathology variation in ONSD measurement.

I look forward to reading the results of this study and hope it will contribute to our understanding of this promising non-invasive marker of ICP.
**Thank you for your thoughtful comments.

Thank you very much for the opportunity to revise our manuscript. We appreciate the constructive critiques of the manuscript and the chance to improve our systematic review. We do truly hope that it will be of interest to the readers of BMJ Open.
Respectfully submitted on behalf of the group.

VERSION 2 – REVIEW

REVIEWER	Llewellyn C. Padayachy Pediatric Neurosurgeon University of Cape Town, Honorary Senior Clinical Research Fellow University of Oxford
REVIEW RETURNED	09-May-2017

GENERAL COMMENTS	The revised manuscript has adequately addressed earlier issues