

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

TITLE (PROVISIONAL)	Global epidemiology and patterns of cerebral venous thrombosis: a systematic review and meta-analysis protocol
AUTHORS	Danwang, Celestin; Mazou, Temgoua Ngou; Tochie, Joel Noutakdie; Tankeu, Ronni; Bigna, Jean Joel

VERSION 1 – REVIEW

REVIEWER	John A. Heit, M.D. Mayo Clinic, USA
REVIEW RETURNED	12-Oct-2017

GENERAL COMMENTS	<p>Danwang and co-workers report a protocol for a systematic review and meta-analysis that aims “to critically synthesize data concerning prevalence, incidence, risk factors, clinical presentation and mortality rate of CVT [cerebral vein thrombosis] in people living in LMICs [low- and middle-income countries]”.</p> <p>Comments to the authors: Although the study aims are important and clinically-relevant, it is doubtful that they can be accomplished due to very sparse published data available, particularly in LMICs. As the authors note, LMICs are the least likely to have the required diagnostic imaging available for distinguishing CVT from the myriad other causes for the non-specific clinical presentation headache, altered consciousness and/or stroke. Thus, I completely agree with the authors’ statement that “the result may not reflect the true burden of CVT in the population of LMICs”. While the study design and proposed analyses are appropriate and well-written, the lack of sound published data is a major flaw in the study that would prevent sound interpretation of the study results.</p>
-------------------------	---

REVIEWER	mohammad Wasay aga khan University karachi
REVIEW RETURNED	16-Oct-2017

GENERAL COMMENTS	<p>CVT literature is limited a comparison of CVT in Upper income countries versus low and middle income countries may be more useful than reviewing only low and middle income countries outcome death and disability, risk factors, age and gender are important comparison prevalence data is limited from LMIC</p>
-------------------------	---

REVIEWER	Thalia Field University of British Columbia, Canada
-----------------	--

REVIEW RETURNED	09-Jan-2018
------------------------	-------------

GENERAL COMMENTS	<p>This is a protocol for a systematic review and meta-analysis addressing incidence and prevalence of cerebral venous thrombosis (CVT) in low- and middle- income countries (LMIC). The authors also plan to examine risk factors, clinical features and case-fatality rates.</p> <p>This work is interesting and will help to fill a knowledge gap to address why reported rates of CVT and prognosis seems to be so very different in LMIC as compared to higher income countries.</p> <p>Some suggestions:</p> <p>Major:</p> <ul style="list-style-type: none"> -The introduction does not fully address the true importance of this work and should be more fully developed. Small reports from low and middle income nations cite rates of CVT that are much higher than those reports from higher income countries. Clarification of rates in low and middle income countries may help to identify distinct risk factors and may help to address modifiable risk factors for the condition. Similarly, reports from Europe and North America rates of death and disability are low and prognosis is deemed to be "good" - however, without excellent postpartum care and stroke unit resources, prognosis may be worse and discrepancies between high and LMIC may help to identify opportunities for improved care. -It is not clear to me from the "Data extraction and management" section what the authors mean by "clinical features" in their objectives (ie. plan to examine "clinical features" of CVT in LMIC). -The authors should include their data extraction form and adapted risk of bias tool as appendices. - The authors in their search strategy have names the individual LMIC they are considering but should clarify what definition they are using for LMIC. -Limitations are mentioned in the abstract but not in the body of the manuscript and should also be included and further elaborated upon. <p>Minor:</p> <ul style="list-style-type: none"> -It was difficult for me to tell - are the authors only including open-access articles or articles provided by authors on request? If this is the case I would suggest that steps be taken to collaborate with a co-investigator with University-funded access to journals and intra-library loan capabilities. -There are several typos in the protocol that should be fixed prior to resubmission.
-------------------------	---

VERSION 1 – AUTHOR RESPONSE

Editor #1

Please ensure that the information provided in the PROSPERO registry is consistent with that provided in your protocol. For example, we noticed that the registry states that you will include studies published between the 1st of January 1990 and the 30st of August 2017, however your protocol

provides an end date of 31st of October 2017. Please also update the PROSPERO registry accordingly.

Authors' Response 1

Thank you for your comment. We have updated the PROSPERO registration accordingly.

Reviewer #1

Danwang and co-workers report a protocol for a systematic review and meta-analysis that aims "to critically synthesize data concerning prevalence, incidence, risk factors, clinical presentation and mortality rate of CVT [cerebral vein thrombosis] in people living in LMICs [low- and middle-income countries]".

Reviewer's comment 1

Although the study aims are important and clinically-relevant, it is doubtful that they can be accomplished due to very sparse published data available, particularly in LMICs. As the authors note, LMICs are the least likely to have the required diagnostic imaging available for distinguishing CVT from the myriad other causes for the non-specific clinical presentation headache, altered consciousness and/or stroke. Thus, I completely agree with the authors' statement that "the result may not reflect the true burden of CVT in the population of LMICs". While the study design and proposed analyses are appropriate and well-written, the lack of sound published data is a major flaw in the study that would prevent sound interpretation of the study results.

Authors' Response 1

Thank you for your comment. Since the number of publications on the topic in LMICs may be limited, we have revised the protocol to conduct a global systematic review.

Reviewer #2

Reviewer's comment 1

CVT literature is limited a comparison of CVT in Upper income countries versus low and middle income countries may be more useful than reviewing only low and middle income countries outcome death and disability, risk factors, age and gender are important comparison prevalence data is limited from LMIC

Authors' Response 1

Thanks for this concern. We will now conduct a global systematic review. Therefore, we will be able to compare data across region by level of income.

Reviewer #3

This is a protocol for a systematic review and meta-analysis addressing incidence and prevalence of cerebral venous thrombosis (CVT) in low- and middle- income countries (LMIC). The authors also plan to examine risk factors, clinical features and case-fatality rates.

This work is interesting and will help to fill a knowledge gap to address why reported rates of CVT and prognosis seems to be so very different in LMIC as compared to higher income countries.

Some suggestions:

Major:

Reviewer's comment 1

-The introduction does not fully address the true importance of this work and should be more fully developed. Small reports from low and middle income nations cite rates of CVT that are much higher than those reports from higher income countries. Clarification of rates in low and middle income countries may help to identify distinct risk factors and may help to address modifiable risk factors for the condition. Similarly, reports from Europe and North America rates of death and disability are low

and prognosis is deemed to be "good" - however, without excellent postpartum care and stroke unit resources, prognosis may be worse and discrepancies between high and LMIC may help to identify opportunities for improved care.

Authors' Response 1

Thanks for this concern. The introduction has been modified and the importance of the work has been further detailed. In order to highlight the differences between low and middle-income countries and developed countries, we thought it necessary to carry out a global review comparing the data obtained in these two different contexts.

Reviewer's comment 2

-It is not clear to me from the "Data extraction and management" section what the authors mean by "clinical features" in their objectives (ie. plan to examine "clinical features" of CVT in LMIC).

Authors' Response 2

Thank you for your concern. By "clinical feature of CVT" we mean the various signs and symptoms of CVT. This item has been added to the "data extraction and management" section and its explained in the objectives as proposed.

Reviewer's comment 3

-The authors should include their data extraction form and adapted risk of bias tool as appendices.

Authors' Response 3

Thank you for your suggestion. The data extraction form and adapted risk of bias assessment tool has been added as additional files.

Reviewer's comment 4

- The authors in their search strategy have names the individual LMIC they are considering but should clarify what definition they are using for LMIC.

Authors' Response 4

Thank you for this concern. Since we will now perform a global systematic review, search strategy will not include name of countries.

Reviewer's comment 5

-Limitations are mentioned in the abstract but not in the body of the manuscript and should also be included and further elaborated upon.

Authors' Response 5

Thank you for your comment. A dedicated section is reserved for limitations of the study below the Keywords, and this section is not a part of abstract, but a separated section as recommended by the journal editorial office.

Reviewer's comment 6

Minor:

-It was difficult for me to tell - are the authors only including open-access articles or articles provided by authors on request? If this is the case I would suggest that steps be taken to collaborate with a co-investigator with University-funded access to journals and intra-library loan capabilities.

Authors' Response 6

Thank you for raising this point. All types of articles will be included (open and non-open access). For articles that will not be open access, we will use HINARI code provided by our university to search the articles concerned in HINARI database. In case of failure, an email will be sent to the corresponding author to provide them.

Reviewer's comment 7

-There are several typos in the protocol that should be fixed prior to resubmission.

Authors' Response 7

Thank you for your comment. We have corrected accordingly.

VERSION 2 – REVIEW

REVIEWER	Thalia Field University of British Columbia
REVIEW RETURNED	20-Feb-2018
GENERAL COMMENTS	<p>Most of my comments have been satisfactorily addressed. I think it is a good idea to examine regional differences in burden of disease and outcomes including higher income countries as well for comparison.</p> <p>I don't think that much will be added by including signs and symptoms in the systematic review. These are well described and well known. One would not expect a regional difference here, I would think, unless there were a tendency towards a particular anatomic location (deep venous system versus cortical vein or isolated sinus, for example) or differences in timing of diagnosis and initiation of therapy. Other clinical features beyond signs and symptoms may be of value, however, as outlined above.</p> <p>There are still a number of typos. The methods in the abstract does not reflect the change to including systematic review.</p> <p>When discussing limitations, the authors should elaborate upon ascertainment bias. Instead of invoking powerful meta-analysis techniques, the authors may want to instead discuss the systematic review approach they are using to augment the meta-analysizable data.</p>

VERSION 2 – AUTHOR RESPONSE

Reviewer #3

Most of my comments have been satisfactorily addressed.

Reviewer's comment 1

I think it is a good idea to examine regional differences in burden of disease and outcomes including higher income countries as well for comparison.

Authors' Response 1

Thank you for your comment.

Reviewer's comment 2

I don't think that much will be added by including signs and symptoms in the systematic review. These are well described and well known. One would not expect a regional difference here, I would think, unless there were a tendency towards a particular anatomic location (deep venous system versus cortical vein or isolated sinus, for example) or differences in timing of diagnosis and initiation of therapy. Other clinical features beyond signs and symptoms may be of value, however, as outlined above.

Authors' Response 2

Thank you for your suggestion. Instead of signs and symptoms, we will report the anatomical location of the lesions, and the delay between the onset of symptoms and initiation of treatment, taking into account the economic context (developed and developing countries).

Reviewer's comment 3

There are still a number of typos

Authors' Response 3

Thank you for your suggestion. The manuscript has been revised accordingly.

Reviewer's comment 4

The methods in the abstract does not reflect the change to including systematic review.

Authors' Response 4

Thank you for this concern. The abstract has been revised accordingly.

Reviewer's comment 5

When discussing limitations, the authors should elaborate upon ascertainment bias. Instead of invoking powerful meta-analysis techniques, the authors may want to instead discuss the systematic review approach they are using to augment the meta-analyzable data.

Authors' Response 5

Thank you for your comment. The limitations section has been revised, and metanalytic techniques that we are planning to use have been furthermore developed and, as well as the ascertainment of bias.