PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	RATIONALE AND DESIGN OF A MULTI-CENTER CROSS-SECTIONAL STUDY FOR THE SCREENING OF PULMONARY HYPERTENSION IN METHAMPHETAMINE ABUSERS (SOPHMA)
AUTHORS	Cheng, Yangyang; Tung, Chi-Kwong; Chung, Albert Kar Kin; Liu, Wan-Wan; Huang, Duo; Chan, Pak Hei; Lam, Ming; Chan, Wai-Chi; SIU, Chung-Wah; Hai, Jo Jo

VERSION 1 - REVIEW

REVIEWER	Lohit Garg Lehigh Valley Health Network, USA
REVIEW RETURNED	11-Nov-2018

GENERAL COMMENTS	The authors have done a commendable job in designing a very appropriate study. Methamphetamine us is prevalent around the globe and is "likely" a cause of drug induced PAH. The exact prevalence of PAH in this high risk group is not defined. The authors with the SOPHOMA study intends to define the prevalence as well as the risk factors for the development of PAH in methamphetamine users. I have few minor comments regarding the study: 1. In page 9, Line 8 the numbering needs to be corrected. 2. The authors have written that they will define the prevalence and type of PAH. It is unclear from the protocol that how will they define the type of PAH, are they going to do the work up for alternative cause for PAH in high risk patients, if negative will it consider idiopathic "Drug induced PAH"? Also If other work up for PAH is positive, would it be considered due to methamphetamine use and included in prevalence or excluded? 3. Please consider including collecting data for prior DVT/PE in demographics.

REVIEWER	John Richards UC Davis Medical Center, Sacramento, California, USA
REVIEW RETURNED	14-Dec-2018

GENERAL COMMENTS	Outstanding study with well-defined study population and outcome measurements. My only suggestions to improve the paper are: 1) Spell out all numbers less than 10 2) on Page 3 line 23 replace "amphetamine" with "methamphetamine" to remain consistent throughout the paper. 3) Change "arrhythmias" to "dysrhythmias" on Page 5 line 28 4) Define "WU" as "Woods units" on Page 5 line 42

REVIEWER	Michael McGee CJohn Hunter Hospital
REVIEW RETURNED	30-Jan-2019

GENERAL COMMENTS	This is a protocol for a multi-center, cross-sectional screening for Pulmonary Hypertension in a difficult cohort (Methamphetamine abusers). The protocol and premise are well constructed, though it remains to be seen if there is a sufficiently large population who agree to be involved to reach any clinically significant conclusions.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s) Reports:

Reviewer: 1

Reviewer Name: Lohit Garg

Institution and Country: Lehigh Valley Health Network, USA

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

The authors have done a commendable job in designing a very appropriate study. Methamphetamine us is prevalent around the globe and is "likely" a cause of drug induced PAH. The exact prevalence of PAH in this high risk group is not defined. The authors with the SOPHOMA study intends to define the prevalence as well as the risk factors for the development of PAH in methamphetamine users. I have few minor comments regarding the study:

1. In page 9, Line 8 the numbering needs to be corrected.

Authors’ response: Thank you very much for your comment. We have corrected the numberings accordingly. – Page 7, paragraph 2, line 4.

2. The authors have written that they will define the prevalence and type of PAH. It is unclear from the protocol that how will they define the type of PAH, are they going to do the work up for alternative cause for PAH in high risk patients, if negative will it consider idiopathic "Drug induced PAH"?

Also If other work up for PAH is positive, would it be considered due to methamphetamine use and included in prevalence or excluded?

Authors' response: Thank you very much for your enquiries.

1) In this study, all diagnostic criteria will be adopted from contemporary guidelines. In brief, pulmonary hypertension is defined by a mean pulmonary artery pressure □25mmHg. The type of pulmonary hypertension will be further classified into group one to group five according to hemodynamic findings of right heart catheterization, clinical presentation, radiological investigation results and other pathological findings. PAH, also known as group one pulmonary hypertension, is defined by a pulmonary capillary wedge pressure (PCWP) ≤15 mmHg and pulmonary vascular resistance (PVR) >3 wood units in the absence of significant left-sided heart disease, severe lung disease or chronic thromboembolic disease. – Page 10, paragraph 2 and Page 11, paragraph 1.

2) For those who have PAH diagnosed, additional workup will be performed to look for other contributory factors of PAH, including connective tissue disorder, human immunodeficiency virus infection and chronic liver disease. – Page 10, paragraph 2 and Page 11, paragraph 1.

3) Our group retain the use of PAH, not 'drug-induced' PAH, as our primary study measure. It is because there is no reliable test that can ascertain, or exclude, the diagnosis of drug-induced PAH. While those aforementioned factors represent possible alternative causes of PAH, they can also be factors that precipitate or perpetuate the development of PAH in methamphetamine users. A similar diagnostic and reporting approach was employed by the DETECT study. As a result, our group will report the prevalence of all PAH in our study population and the contributory factors objectively. – Page 11, paragraph 2.

Please consider including collecting data for prior DVT/PE in demographics.

Authors' response: Thank you very much for your comment. We have included prior DVT / PE in data collection accordingly. We have also more detailed descriptions of the parameters that will be included in data collection. Page 21, Table 2.

Reviewer: 2

Reviewer Name: John Richards

Institution and Country: UC Davis Medical Center, Sacramento, California, USA

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

Please leave your comments for the authors below

Outstanding study with well-defined study population and outcome measurements.

My only suggestions to improve the paper are:

1) Spell out all numbers less than 10

Authors' response: Thank you very much for your comment. We have spelled out all numbers less than 10 in the manuscript.

2) on Page 3 line 23 replace "amphetamine" with "methamphetamine" to remain consistent throughout the paper.

Authors' response: Thank you very much for your comment. We have changed it to methamphetamine accordingly. – Page 7, paragraph 2, line 3.

3) Change "arrhythmias" to "dysrhythmias" on Page 5 line 28

Authors' response: Thank you very much for your comment. We have changed it to dysrhythmias accordingly. – Page 4, paragraph 1, line 11.

4) Define "WU" as "Wood units" on Page 5 line 42

Authors' response: Thank you very much for your comment. We have changed it to Wood Units accordingly. – Page 10, paragraph 2, line 9.

Reviewer: 3

Reviewer Name: Michael McGee

Institution and Country: John Hunter Hospital

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

Please leave your comments for the authors below

This is a protocol for a multi-center, cross-sectional screening for Pulmonary Hypertension in a difficult cohort (Methamphetamine abusers). The protocol and premise are well constructed, though it remains to be seen if there is a sufficiently large population who agree to be involved to reach any clinically significant conclusions.

Authors' response: Thank you very much for your comment.

VERSION 2 – REVIEW

REVIEWER	Lohit Garg Lehigh Valley Health Network, USA
REVIEW RETURNED	03-May-2019

GENERAL COMMENTS	The authors have made satisfactory changes to the manuscript as requested. The study is well constructed, though it remains to be seen if the authors will be able to enroll enough patients who agree to be involved to reach any clinically significant conclusions.