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.

This paper was submitted to the JECH but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	RATIONALE AND DESIGN OF THE PAN AFRICAN PULMONARY HYPERTENSION COHORT (PAPUCO) STUDY: IMPLEMENTING A CONTEMPORARY REGISTRY ON PULMONARY HYPERTENSION IN AFRICA
AUTHORS	Thienemann, Friedric; Dzudie, Anastase; Mocumbi, Ana; Blauwet, Lori; Sani, Mahmoud; Karaye, Kamilu; Ogah, Okechukwu; Mbanze, Irina; Mbakwem, Amam; Udo, Patience; Tibazarwa, Kemi; Ibrahim, Ahmed; Burton, Rosie; Damasceno, Albertino; Stewart, Simon; Sliwa, Karen

VERSION 1 - REVIEW

REVIEWER	Rui Baptista Cardiology Department, Centro Hospitalar e Universitário de Coimbra Faculty of Medicine, University of Coimbra Portugal
REVIEW RETURNED	06-Aug-2014

GENERAL COMMENTS	The authors are to be praised for implementing the first continent-wide registry of pulmonary hypertension in Africa. Due to the intrinsic limitations of the healthcare systems in Africa, this registry does not demand a right heart catheterization for the confirmation of PH and its etiology. This is the major limitation of this registry, but has to be seen in the light of the limitations of the countries entering the registry. Echocardiography will be cornerstone in this study and will be used for diagnosis and etiological assessment of the different PH etiologies. In fact, in the introduction (Page 9, line 32), there is some confusion as the term "idiopathic PH" is used. If pulmonary hypertension is due to pulmonary arterial hypertension then the term PAH should be used (group 1 Dana Point) and if it is idiopathic then we have "idiopathic PAH". Having in consideration that there is no evidence-based information about pulmonary hypertension in Africa, and taking into account the limitation posed by the absence of right heart catheterization, I believe that the results of this multi-center work may have impact on the knowledge of PH as an "echocardiographic" hemodynamic disease.

REVIEWER	Robin Condliffe Sheffield Pulmonary Vascular Disease Unit Royal Hallamshire Hospital Sheffield United Kingdom
REVIEW RETURNED	08-Aug-2014

GENERAL COMMENTS	I think this is a very important undertaking. The major criticism as a paper for publication is the lack of data - it is essentially a study protocol. I have a few specific points: 1. Diagnosis of PH. Reference is made to the ESC/ERS approach (which is: likely normal if sPAP <36mmHg, probable 36-50 if other features of PH on echo, probable if >50 mmHg, using an estimate of RAP of 5mmhg), however in your study you have chosen to define by if sPAP > 35mmHg, which is a simplification of the ESC approach and may lead to over-diagnosis of PH. I was also unsure how you were planning on estimating RAP. 2. Clearly a major issue in Africa is how to properly assess patients in the context of a lack of resources. The primary aim of the study is to define the make-up of PH within the continent. Without routine serological testing for schistsomiasis or HIV, spirometryand imaging for lung disease and VQ or CTPA for chronic thromboembolic disease then this will be very difficult to perform robustly. This unavoidable but major limitation needs to be emphasised further. 3. Patient selection. There is likely to be significant bias in terms of patients accessing health care at your PH centres and this will have a significant effect on your ability to robustly describe the contribution of the different forms of PH to the overall burden of the conditoin in the continent. 4. Patient numbers. I was unsure how long recruitment is planned for, if there is a target number and how you will approach regional differences in recruitment in the different regions of the continent. 5. Sub-studies. Little explanation is made regarding the different substudies that are planned. I think this is a very important undertaking although there are clear limitations in accurately defining PH and accurately phenotyping the form of PH, especially in view of limitations in investigations. The manuscript submitted is very much a protocol for your study and if not accepted by the current journal I wonder whether a submission to pulmonary circulation may be warranted.

REVIEWER	Gregory J. Kato, MD Division of Hematology-Oncology, Department of Medicine Pittsburgh Heart, Lung, Blood, and Vascular Medicine Institute University of Pittsburgh 200 Lothrop Street, BST E1240

	Pittsburgh, PA 15261 USA
REVIEW RETURNED	14-Aug-2014

GENERAL COMMENTS	This paper is very well written and presents the plan for a pan-African Pulmonary Hypertension Cohort research project. No new research data is presented, and it must be an editorial decision whether new data is a prerequisite for publication in the journal. There are no other major flaws in this manuscript. Minor Comments 1. Page 16, first line: "PAP" should be "mean PAP" 2. Page 16, "PH" should be "pulmonary arterial hypertension" because PVR >3 Wood units refers only to pulmonary arterial hypertension, and not pulmonary venous hypertension or therefore pulmonary hyeprtension in general. 3. Page 16, third line "envelops" should be "envelopes" 4. Page 17, second line: "PAPS" should be "PASP" 5. Page 19, "written inform consent" should be "written informed consent" 6. It would be interesting if the authors presented preliminary data from patients enrolled so far, but I understand if they prefer to withhold this until higher enrollment develops with consequent higher statistical power.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Robin Condliffe
Institution and Country Sheffield Pulmonary Vascular Disease Unit
Royal Hallamshire Hospital
Sheffield
United Kingdom
Please state any competing interests or state ‘None declared’: Non declared

I think this is a very important undertaking. The major criticism as a paper for publication is the lack of data - it is essentially a study protocol. I have a few specific points:

1. Diagnosis of PH. Reference is made to the ESC/ERS approach (which is: likely normal if sPAP <36mmHg, probable 36-50 if other features of PH on echo, probable if >50 mmHg, using an estimate of RAP of 5mmhg), however in your study you have chosen to define by if sPAP > 35mmHg, which is a simplification of the ESC approach and may lead to over-diagnosis of PH. I was also unsure how you were planning on estimating RAP.

We are aware that low pressures between 36 and 50 mmHg bear the risk of over-diagnosing pulmonary hypertension using Echocardiography for diagnosis. We work in referral system heath care and patients have been referred due to persisting symptoms of right heart failure as outlined per algorithm. We did not want to exclude these symptomatic patients from the registry even though in

cases the pressure is below 50 mmHg. In a previous study we also used 35 mmHg as cut-off (Stewart, European Journal of Heart Failure, 2011) we have added this reference to the manuscript. RAP is estimated by respiratory variation size of the vena cava inferior in M-mode. We have added this to the manuscript with reference.

2. Clearly a major issue in Africa is how to properly assess patients in the context of a lack of resources. The primary aim of the study is to define the make-up of PH within the continent. Without routine serological testing for schistosomiasis or HIV, spirometry and imaging for lung disease and VQ or CTPA for chronic thromboembolic disease then this will be very difficult to perform robustly. This unavoidable but major limitation needs to be emphasised further.

Thank you for your valid comments. This has been highlighted in the limitations sections. Please see Table 1 with diagnostic infrastructure of the participating centres. We did not want to exclude centres that do not have the entire battery to work up PH patients. This would lead to a wrong picture of PH in Africa.

3. Patient selection. There is likely to be significant bias in terms of patients accessing health care at your PH centres and this will have a significant effect on your ability to robustly describe the contribution of the different forms of PH to the overall burden of the condition in the continent.

Thank you for your comment. This is an inherent problem with all registries. PAPUCO is not aimed at measuring the prevalence of PH of certain risk groups according to the updated Dana Point 2008 classification, but to define the broad spectrum in PH as seen at referral centres in Africa.

4. Patient numbers. I was unsure how long recruitment is planned for, if there is a target number and how you will approach regional differences in recruitment in the different regions of the continent.

We aim to recruit consecutive patients as seen in the different centres over a period of 3 years. PAPUCO is a low-cost-research project as we have not been able to secure a larger grant funding this project done in several African countries. If funding can be secured we will continue for another 3 to 5 years and implements innervations on top of the registry. Not all centres will contribute equally to the registry due to regional differences of risk factors but also referral structures within the participating centres.

5. Sub-studies. Little explanation is made regarding the different substudies that are planned.

We have outlines the different sub-studies on Echo, LHD, RHD, CHD and HIV on page 18/19, however we are unable to elaborate further on these stub studies within this manuscript.

I think this is a very important undertaking although there are clear limitations in accurately defining PH and accurately phenotyping the form of PH, especially in view of limitations in investigations. The manuscript submitted is very much a protocol for your study and if not accepted by the current journal I wonder whether a submission to pulmonary circulation may be warranted.

Reviewer Name Gregory J. Kato, MD
Institution and Country Division of Hematology-Oncology, Department of Medicine
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Please state any competing interests or state ‘None declared’: None declared.

This paper is very well written and presents the plan for a pan-African Pulmonary Hypertension Cohort research project. No new research data is presented, and it must be an editorial decision whether new data is a prerequisite for publication in the journal. There are no other major flaws in this manuscript.

Thank you for your comments. We have submitted this publication as a protocol without result. To make this more clear, the editor has requesting to change the title of the manuscript highlighting that it is a protocol. The new title reads: “RATIONAL AND DESIGN OF THE PAN AFRICAN PULMONARY HYPERTENSION COHORT (PAPUCO) STUDY: IMPLEMENTING A CONTEMPORARY REGISTRY ON PULMONARY HYPERTENSION IN AFRICA”

Minor Comments

1. Page 16, first line: "PAP" should be "mean PAP"

Thank you for pointing this out, we have rectified this in the manuscript.

2. Page 16, "PH" should be "pulmonary arterial hypertension" because PVR >3 Wood units refers only to pulmonary arterial hypertension, and not pulmonary venous hypertension or therefore pulmonary hypertension in general.

Thank you for pointing this out, we have rectified this in the manuscript and also changed PH to PAH for all group 1 PAH.

3. Page 16, third line "envelops" should be "envelopes"

Thank you for pointing this out, we have rectified this in the manuscript.

4. Page 17, second line: "PAPS" should be "PASP"

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5. Page 19, "written inform consent" should be "written informed consent"

Thank you for pointing this out, we have rectified this in the manuscript.

6. It would be interesting if the authors presented preliminary data from patients enrolled so far, but I understand if they prefer to withhold this until higher enrolment develops with consequent higher statistical power.

Thank you for your understanding

No further comments.