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External Review of PhD Thesis of Dr Aigerim Mullen

entitled:

“Diagnosis and comprehensive therapy of pulmonary arterial hypertension in children with congenital left-to-right shunt”

Presented for the degree of **Doctor of Philosophy (PhD)** in the speciality “Medicine” 6D 110100

Supervisor: Nurgaliyeva Zh.Zh. (Kz)

Co-Supervisor: Professor Ghazwan Butrous (UK)

Dr Aigerim Mullen's doctoral thesis concerns the approach to diagnosis and comprehensive therapy of pulmonary arterial hypertension in children with congenital left-to-right shunt in the Kazakhstan Region of Central Asia.

For my assessment, I have reviewed the following:

- English translations of Materials and methods, Discussion, Conclusions and Recommendations
- Results from the thesis, as presented to me first-hand by Dr Mullen through explanation of the data and graphs within the original language thesis
- The announcement by Asfendiyarov Kazakh National Medical University of the defence of the thesis including validation of publications
- Statement by the UK supervisor

1. Relevance of the topic

Pulmonary arterial hypertension (PAH) is a well-recognized complication of congenital heart disease (CHD), especially in patients with left-to-right shunts and is associated with increased mortality and morbidity which is reflected in a substantial increase in health service utilisation. Prevalence of PAH-CHD undoubtedly varies and there is paucity of data from Central Asia. The population of adult patients with PAH-CHD is also growing worldwide and represents a significant challenge for healthcare systems worldwide despite recent advancements in treatments. Dr Mullen's thesis presents a controlled, nonrandomised, clinical observational, single centre study of PAH-CHD in the Scientific Centre of Paediatrics and Paediatric Surgery, Almaty, Kazakhstan. The research subject of this thesis is therefore of importance in an International context. It is also relevant in understanding the provision of local healthcare systems for diagnosis and treatment of PAH-CHD along with related educational demands.

2. Scientific results

The results are represented in valid scientific manner.

Overall graphs and figures are well presented with minor caveats detailed in critique and remaining data appears to be adequately described in text.

Demographics are very well detailed throughout providing a sound basis for comparison of this study with similar cohorts in other countries. Causes of PAH-CHD in the described population are well documented and important differences between the two groups (treated and untreated) are accurately presented and defined.

Dr Mullen, then presents the differences between retrospectively analysed (non-treated) patients and prospectively collected (treated) groups of patients in terms of pre- and postoperative Echo and Cath data (including AVRT), length of stay in CICU and overall hospital stay.

3. Validity of the scientific conclusions and recommendations

The conclusions presented and reviewed are valid statements based on the nature of the results as presented to me. Recommendations to me seem straightforward, with the caveat that recommendation numbers 7, 8 are more speculative and can only be validated by future study. Such research would be warranted however, based on the findings presented in Dr Mullen's thesis.

4. Scientific novelty of the scientific conclusions and recommendations

In my opinion, this work is novel and original and no doubt advances scientific knowledge in the field of paediatric PAH-CHD, specifically in the region of Central Asia and Kazakhstan. In terms of impact, as reported, this work has already led to the adaptation of international guidelines and a new practical algorithm for the treatment of PAH in children with congenital left to right shunts.

5. Evaluation of the internal coherence and cohesion of the results

The thesis is presented in a logical and coherent manner throughout. There is excellent development and exploration of the data and as indicated in (3) above the conclusions and recommendations derived follow rationally from the results.

6. Determination of the results for the problem solution

The results as presented appear appropriate for the aims of the thesis, and given the data available and collected by Dr Mullen.

7. Confirmation of the fulfilment of publication's requirements

The work presented has already resulted in multiple publications and abstracts which I see from the announcement of the thesis defence have been validated by the host University.

8. Comments and critique of the thesis content and design

The study design, chapter designation and presentation of material throughout is of high standard. The thesis is accurately and well referenced throughout. One minor recommendation I have is that the y-axes of all graphs should be labelled so that the figures can be immediately interpreted by the reader, without knowledge of the legend or text. Confidence intervals have been presented for some of the data but I would also recommend that they are included for presentation of proportions, (ie: in the latter sections of the work), particularly given the small sample size. In this way, the relevance of the proportions presented would be immediately apparent.

9. Conclusion on adequacy and concordance of the dissertation and recommendation for the PhD degree award

In conclusion, the thesis is well presented and structured and undoubtedly advances the scientific understanding of pulmonary hypertension in congenital heart disease, specifically in a regional context. It promotes understanding of the regional diversity of congenital heart disease and its effect on the pulmonary vasculature arrives at practical recommendations for its treatment. In my opinion, the reviewed thesis fulfils all criteria of valid scientific research and I recommend that thesis is ready to be publicly defended, in front of the appropriate committee.



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