Reviewer's report

**Title:** The effect of Bosentan on exercise capacity in Fontan patients; rationale and design for the TEMPO study

**Version:** 3  **Date:** 18 January 2013

**Reviewer:** Yves d’Udekem

**Reviewer's report:**

The authors are initiating a large-scale study on the effect of Bosentan on the exercise capacity of patients who have undergone Fontan surgery. They present a well-written manuscript of a well-designed study.

**Discretionaly Revisions**

The question that they are trying to solve is important and the community of practitioners taking care of this population would be very interested to have the results from their study. Their track record is excellent and they are likely able to recruit the planned number of patients. From my personal experience and the population estimates I have consulted, they are also likely to investigate during the course of their study the majority of the potential candidates for this study. Therefore, it is likely that they will not be able to recruit a lot of additional patients after the completion of this initial study.

I personally believe that the target of a 20% increase of the peak VO2 is optimistic and that they may fail to demonstrate this change in these Fontan patients. And I am afraid that despite the large number of patients enrolled this population this population will still be too small to prove the null hypothesis. From published indirect evidence and my personal experience, I believe that the maximal exercise capacity of Fontan patients is limited by a fixed resistance in the Fontan circuitry that cannot be overcome by an increase in cardiac output or improved by pulmonary vasodilators. I had personally thought about initiating the same study but was discouraged by the amount of work necessary with the perspective of yielding negative results. Therefore I would encourage the authors to think hard at performing investigations that would enable them to explain why negative findings would occur. Imaging of the Fontan circuitry would be necessary to this end, and it is possible that smaller or distorted Fontan circuit would not allow improvement in the exercise capacity of these patients.

In this view, if standardized serial assessment of the Fontan circuitry is performed in their region and they intend to use these examinations to screen patients before to enrolment, I would specify this fact in the manuscript.

**Minor Essential Revisions**

On table 1 “systolic blood pressure below 80% of reference” is specified, but no references are given in the manuscript.

Similarly, “obstruction of the TCPC circulation” is undefined.
On the table 2, the denomination “tunnel” is unclear. Do they refer to the type of Fontan, atropulmonary connection/lateral tunnel/extra-cardiac conduit? This is the reason I personally try to avoid the term “TCPC” which is confusing (at least for surgeons).

There is no mention of any approval of the project by any Swedish Ethics Committee.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests