Reviewer's report

Title: Cardiovascular Risks and Elevation of Serum DHT Vary by Route of Testosterone Administration; a Systematic Review and Meta-analysis

Version: 1 Date: 30 September 2014

Reviewer: Lin Xu

Reviewer's report:

This manuscript describes meta-analyses of randomized, placebo controlled, clinical trials (RCTs) for testosterone replacement therapy (TRT) and DHT levels in non-RCTs for TRT related cardiovascular event. The authors described why the methodology used for their meta-analyses might be better than recent reports. They performed a separate analysis of treatment-related changes in circulating T and DHT, and attempted to draw the two strands together in a unifying conceptual framework which relates adverse events to mode of delivery via increments in DHT. The work is methodical and the approach is interesting. However, there are several areas of major concern which need to be rectified.

Major problems:

1. Abstract: The author concluded that oral TRT produces significant CV risk. However, the study included only 4 oral studies, of which two did not show any increase in CV events and 2 others did.

2. Abstract: It is confusing to refer to the statement of "non-significant directional trends". If there were no significant differences, the authors should refrain from implying such differences may exist. The authors implied that greater risk with oral T may be due to greater elevation of DHT. However, there was no increase in CV risk with transdermal T despite comparable elevation of DHT, so the importance of the increment in DHT remains unclear.

3. The included studies did not have CV events as a pre-specified end point.

4. Given the authors stated that studies included in this meta-analysis reflect less publication bias, the authors are suggested to present a funnel-plot to check for the existence of publication bias, and present the results using trim-and-fill analysis, if applicable.

5. Not clear whether the sensitivity analysis was done. If not, please remove the "sensitivity analysis" session in Methods to avoid confusion and add a limitation of the lack of sensitivity analysis in Discussion.

6. The discussion section is weak and needs to be improved, especially no discussion on study limitations or strengths found.

7. Two of the biggest trials (ref. 7 and 32) were stopped early, how could this have affected your results?

8. How are the Pre-Post treatment fold increases in T/DHT being calculated in Table 3? For example, 3.43 versus 0.99 comes to a 5.5-fold increase and 2.16
versus 0.62 comes to a 6.6-fold increase?

9. Given the discrepancies in assay methods (LC-MS/MS, GC-MS, RIA, fluoro-immuno assay, or others) in the Online file 5, comparison of DHT levels measured by a variety of methods may not be valid. The authors need to specify this and consider it as a limitation.

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.