Reviewer’s report

Title: "Resistant Hypertension On Treatment (ResHypOT), Sequential nephron blockade compared to dual blockade of the renin-angiotensin-aldosterone system plus bisoprolol in the treatment of resistant arterial hypertension: study protocol for a randomized controlled trial"

Version: 1 Date: 29 Sep 2017

Reviewer: Rustam Salman

Reviewer’s report:

Please note that this report is for the Original submission.

1. Thanks for a nicely formatted and clearly-presented manuscript

2. There is no mention in the introduction about the existing evidence in support of approaches to management of resistant hypertension. You can sacrifice much of the pathophysiological explanation for the much more important evidence from systematic reviews and meta-analyses for current therapeutic management. Please cite Cochrane and other high quality systematic reviews to describe (a) what standard practice is, and (b) evidence that the therapeutic uncertainty that you seek to address has not already been resolved.

3. Please also mention in the introduction whether there are any similar ongoing trials addressing the same therapeutic uncertainty. You can determine this from trial register searches.

4. Is there any evidence that patients or their carers have determined that this therapeutic approach is a research priority (see http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)62229-1/abstract)?

5. The method of randomisation is not adequately described. Please say what method you use to do this, and more clearly how allocation is concealed.

6. You describe four co-primary outcomes (Reduction of systolic BP, diastolic BP, mean BP and pulse pressure after 12 weeks of treatment). Surely this is too many for an 80-patient trial? Your sample size calculation is based on diastolic BP, so shouldn't this be your single primary outcome? If you have 4 co-primary outcomes, you need to adjust your level of statistical significance for this. Please include a response from your statistician on this point.

7. Please confirm the trial status: is it still recruiting?

8. I am not sure why several sections are highlighted in yellow. Please explain, or remove.

9. In some places, English language needs to be corrected. If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising
this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES-HS) and American Journal Experts (http://bit.ly/AJE-HS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and our Writing resources (http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English.

**Level of interest**
Please indicate how interesting you found the manuscript:

An article of importance in its field

**Quality of written English**
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Acceptable

**Quality of figures**
All images and figures within the manuscript should be genuine i.e. without evidence of manipulation. No specific feature within an image may be enhanced, obscured, moved, removed, or introduced. If you have concerns about the veracity of the figures you should choose the first option below.

**Statistical review**
Is it essential that this manuscript is seen by an expert statistician? If so, please give your reasons in your report.

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

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