**Author’s response to reviews**

**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"

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**Version:** 2 **Date:** 27 Oct 2017

**Author’s response to reviews:**

Editor's report:

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

Re: Thank you.
2. There is no mention in the introduction about the existing evidence in support of approaches to management of resistant hypertension.

Re: The challenge lies in building an effective regimen in terms of blocking most of the implicated and individualized pathophysiological pathways according to patient profile, lifestyle, comorbidities and even financial limitations. In addition, the optimal combination should be well tolerated by the patient, with minimal adverse events to ensure long-term adherence to therapy. (Pharmacotherapy for resistant hypertension in adults) (Charan, Chaudhari et al. 2017)

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.

Re: However, some resistant hypertensive patients, despite treatment with a three-drug regimen need at least four antihypertensive agents to gain adequate blood pressure control (Daugherty 2012). (Circulation. 2012 Apr 3; 125(13): 1635–1642. Published online 2012 Feb 29. Incidence and Prognosis of Resistant Hypertension in Hypertensive Patients Stacie L. Daugherty, MD MSPH,1,2 J. David Powers, MS,2 David J. Magid, MD, MPH,1,2 Heather M. Tavel, BS,2Frederick A Masoudi, MD, MSPH,1,2,3 Karen L. Margolis, MD, MPH,4 Patrick J O’Connor, MD, MPH,4 Joe V. Selby, MD, MPH,5,6 and P. Michael Ho, MD, PhD1,2,7)(Daugherty, Powers et al. 2012)

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.

Re. There are no similar trials in progress.

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)?
Re: Regarding the recommendations on research priorities published by Professor Iain Chalmers (The Lancet Volume 383, No. 9912, p156–165, 11 January 2014), we can state that studies of the pathophysiology of resistant hypertension that include volume overload have previously been published by other authors. This is the basis of this study. (Chalmers, Bracken et al.)

With regard to funders of the research project, we reiterate the lack of public or private funding for this project. A systematic research has already been performed and we concluded that this comparative intervention represents a challenge involving different priorities of additional therapeutic approach.

Finally, in the literature projects with similar designs but using other drugs have been published.

(Sequential nephron blockade versus sequential renin–angiotensin system blockade in resistant hypertension: a prospective, randomized, open blinded endpoint study
Journal of Hypertension. 30(8):1656–1664, AUG 2012 Guillaume Bobrie; Michael Frank et.al. (Bobrie, Frank et al. 2012)

True antihypertensive efficacy of sequential nephron blockade in patients with resistant hypertension and confirmed medication adherence
Journal of Hypertension. 33(12):2526–2533, DEC 2015 Hélène Beaussier; Pierre Boutouyrie, et.al. (Beaussier, Boutouyrie et al. 2015)

However, a study of a Brazilian population and the use of other drugs not tested in these studies reinforce the importance of our study.

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.

Re: Allocation: Randomized

Intervention Model: Parallel Assignment

Masking: None (Open Label)

Primary Purpose: Treatment

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.
Primary Outcome Measures:

- Office systolic blood pressure (SBP) and diastolic blood pressure (DBP) at week 20, measured with an average blood pressure of 3 measurement with oscillometric device [Time Frame: at week 20]

Secondary Outcome Measures:

- Efficacy: office mean blood pressure (MBP) at week 20, measured with an average blood pressure of 3 measurements using an oscillometric device [Time Frame: at week 20]
- Efficacy: office pulse pressure (PP) at week 20, measured with an average blood pressure of 3 measurements with an oscillometric device [Time Frame: at week 20]
- Efficacy: mean 24 hours SBP and DBP at week 20 measured with an ABPM device [Time Frame: at week 20]
- Safety and tolerability: [Time Frame: during the study]
- During the study BP will be evaluated every 4 weeks by office blood pressure measurement in order to detect hypotension) [Time Frame: every 4 weeks]

Please include a response from your statistician on this point.

Re: The sample size was calculated to demonstrate antihypertensive efficacy with the addition of drugs in each arm. Reduction of SBP and/or DBP.

There will be no need to adjust significance for the primary outcomes.

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

Re: Work in progress, still recruiting, not finalized.

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

Re: I agree

References:


