Author’s response to reviews

Title: Prognosis of patients with apparent treatment resistant hypertension - A feasibility study

Authors:

Peter Hayes (peter.hayes@nuigalway.ie)
Hannah Kielty (h.kielty1@nuigalway.ie)
Monica Casey (monica.casey@nuigalway.ie)
Liam Glynn (Liam.Glynn@ul.ie)
Gerard Molloy (gerry.molloy@nuigalway.ie)
Hannah Durand (H.DURAND1@nuigalway.ie)
John Newell (john.newell@nuigalway.ie)
Andrew Murphy (andrew.murphy@nuigalway.ie)

Version: 1 Date: 18 Dec 2017

Author’s response to reviews:

Dear Editor,

Thank you for considering the publication of our research paper in the BMC-Pilot and Feasibility studies.

I would also like to thank all reviewers for their constructive advice.

With regard to the specific points of concern raised by each reviewer, we have pasted the relevant reviewer text in ‘black’ and our changes or discussions in ‘track changes/red’ below. We have also underlined all updated text in the re-submitted manuscript. Furthermore I include a red/black copy of the reviewers response in the attached PDF.
Just to state, we have had the publication based on our entire cohort (prevalence study) accepted for publication in the BJGP last month- I enclose submission re this directly to editor.

I again thank you for your time in considering our submission for publication in the BMC-Pilot and Feasibility studies Journal.

I hope to hear from you soon

Best wishes

Dr Peter Hayes

(On behalf of all authors)

Your manuscript "Prognosis of patients with apparent treatment resistant hypertension - A feasibility study" (PAFS-D-17-00147) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in Pilot and Feasibility Studies, once you have carried out some essential revisions suggested by our reviewers.

-Thank you

One issue that has been highlighted by two of the reviewers is worth elaborating on. The practices you selected performed remarkably well and this feasibility study certainly encourages a further follow up major cohort study. It would, however, be helpful to the reader if you gave details on what you will do if future practices do not perform to the standard these three seem to have. A major advantage of publishing in Pilot and feasibility studies is that it gives you an opportunity to alert fellow researchers of these pitfalls, glitches, unexpected consumers of time and resources, so please feel free to elaborate.

-Thank you, we will amend

Please also check four references as they appear to be incomplete and cannot be validated:

Myat, Calhoun , NICE and Glynn.

-These have been checked and revised
Reviewer reports:

Reviewer #1: This was a feasibility study conducted within three general practices to inform the development of a larger cohort study aimed at investigating prognosis of patients with resistant hypertension. Specifically it evaluated participation of practices and patients, availability of outcome measures and data collection duration time and presented some results for outcomes of interest in this smaller sample.

ONE

This study appears to lack important details about the objective of the full cohort study and its data requirements which makes it difficult to understand if the data collection and other processes reported in the feasibility study are adequate.

-We regret any confusion and accordingly have rewritten the final paragraph of the introduction as follows:

“Previously, in a cross-sectional study of 6,691 patients with hypertension in sixteen Irish general practices, we identified 646 patients in Irish general practice with aTRH, whose files were individually reviewed, and in whom, pseudo-resistance was also examined (INTRODUCE DOI BJGP). These 646 patients therefore represent a unique general practice cohort of patients with comprehensive assessment for true treatment resistant hypertension. It is planned to conduct a future prognostic cohort study of these 6,691 patients, to compare those with apparent treatment resistant hypertension and those with simple hypertension. In anticipation of this, we conducted a feasibility study to determine participation of practices and patients, availability and frequency of outcome measures and data collection times required.”

TWO

It is unclear as to why this more manual, labour intensive data collection and study approach and smaller sample size is advantageous over the numerous, more efficient, prior studies investigating this issue which utilized large electronic databases and had large cohort sizes.

-All previous studies have been unable to adequately delineate the various apparent treatment resistant hypertension cohorts into those with true-treatment resistant hypertension and those with pseudo-resistance. This is largely because pseudo-resistance has only been examined in most studies in a piecemeal fashion- some studies looking at white coat hypertension alone, and
others only examining dosing or adherence alone. Our key distinguishing feature is in examining all three major causes of pseudo-resistance (white coat hypertension, inadequate dosing and medication adherence) in the same cohort. This can only be done through manual extraction of data from patient’s files. Many large electronic insurance databases are also associated with an intrinsic selection bias - including only those who can afford health insurance.

These points are more comprehensively discussed and described in our parallel paper, just recently published in the British Journal of General Practice, entitled - The prevalence of treatment resistant hypertension with consideration of pseudo-resistance and morbidity (BJGP DOI to be added). This reference is now included in the paper also.

I have outlined my main points below:

Background

THREE

Please add page numbers:

-Now added.

FOUR

Line27-28 High level evidence? Please explain or rephrase. It could be argued that a retrospective cohort study from insurance claims data is not high level evidence given the limitations listed by the author but if the author believes this is high level evidence what is the justification for changing to the study design proposed.

-This was a confusing use of language - apologies.

We have now re-phrased the sentence to:

“In a key study, Daugherty (5) provided the best evidence to date with an outcomes based study on the longitudinal assessment of a large cohort of patients with aTRH (n= 3,960).”
FIVE

Please explain what is meant by dosing? Do you mean they failed to account for the doses of medications used?

-Dosing is the quantity of medicine taken at a single time. In this context, it would mean the quantity of anti-hypertensive medication taken by each patient every time they take the drug that has been prescribed. The quantity of the anti-hypertensive dose prescribed is often sub-optimal and this is often attributed to physician inertia to up-titrate doses. Blood pressure in these instances can remain high, whereas increasing drug doses to higher levels, may help.

SIX

It needs to be made explicitly clear why previous studies examining prognosis of patients with TRH using electronic databases have been limited and exactly why a more labour intensive practice based prospective cohort is necessary with substantially fewer patients than previous studies.

-See point TWO above.

SEVEN

Please give details of what the full cohort study will investigate in the introduction. What is the objective? This is necessary to set the scene.

-See point ONE above.

Methods

EIGHT

Reviewing the records of every patient who uses an anti-hypertensive medication manually seems very labor intensive given the wide spread use of these agents- please comment.

-See point TWO above.
Also how was it determined if they were hypertensive? Although this is mentioned in the introduction the definition used in this study needs to be explicit in the methods.

-We have amended this section as follow:

Each practice ran a standard ATC drug search identifying patients on any possible hypertensive medications as defined by the British National Formulary 69TH Edition ([https://www.amazon.com/?/British-National-Formulary-BNF-69/dp/0857111566](https://www.amazon.com/?/British-National-Formulary-BNF-69/dp/0857111566)). Two researchers (PH & MC), in conjunction with the practices, then reviewed the record of each individual patient who was reported as being on one or more hypertensive medications and determined if they were hypertensive or not, had a previous ambulatory blood pressure measurement or not, and what hypertensive medications and doses they were currently receiving. Patients were identified as being hypertensive if this diagnosis was recorded in clinical notes by their own GP or if they had the appropriate diagnosis code recorded in the patient file (i.e. International Classification of Primary Care codes for hypertension-K87, K87).” This work fulfilled for the general practitioners, the Irish Medical Council requirement to conduct an annual audit.

In the introduction it was mentioned that dosing was not considered in previous studies. There was no mention in this study about assessing doses of medications from the patient medical records?

-Dosing is mentioned to highlight the distinguishing feature of this cohort. Dosing is comprehensively discussed in our parallel paper, just recently published in the British Journal of General Practice, and entitled - The prevalence of treatment resistant hypertension with consideration of pseudo-resistance and morbidity (BJGP DOI to be added). This reference is now included in the paper also.
ELEVEN

Cohort entry date? Will patients be followed up from the same defined point in the disease course to ensure a precise estimate of prognosis? There was no mention of follow up time for the feasibility study in the methods or dates of follow-up?

-Thank you for highlighting this limitation of our work. We now explicitly state in the methods that: “No start date for the diagnosis was recorded - this is not therefore an incident cohort.”

and state in the discussion, as a limitation, that

-“Finally, the cohort was assembled in a cross sectional study and not as an incident cohort with no recorded date of diagnosis. “

TWELVE

Patient characteristics: this should be in the results.

-Revised as suggested.

THIRTEEN

Please state the proportions that have true TRH vs apparent or pseudo TRH among the cohort of 646 patients. These groups are very different and considering these differences when designing the study is important.

-This is now recorded in Tables 1+2.

FOURTEEN

More information is needed on outcome ascertainment in the practices. There is no mention of ensuring outcomes occurred after TRH was first diagnosed.

-See point ELEVEN above.
FIFTEEN

Cohort study design and analysis: based on the study by Daugherty et al. (and your previous study on multi-morbidity and CV outcomes, which informed the current study) a comparator group, was used to compare outcomes in those with TRH versus non-TRH. It is not clear how informative this study will be without this. If a comparator group is to be used how will it be defined and data collected?

-We have now inserted an additional paragraph in the methods section which addresses this key issue:

“Power calculation

Table 3 illustrates the outcomes events for patients with apparent treatment resistant hypertension over a median of 1.9 years. Daugherty et al., for their main composite outcome over 3.8 years, found that 18% and 13.5% of patients with apparent treatment hypertension and simple hypertension respectively had the outcome. 8.3% of our cohort had the equivalent of Daughtery’s composite outcome and 17% a combination of all cardiovascular events. This suggests that a review of our entire original cohort over four years will result, at least, in similar outcome proportions to those of Daugherty.

Taking our original cohort of 6,045 patients with simple hypertension and 645 patients with aTRH, allowing for a loss to follow up of 10% and applying the proportions of 18% and 13%, with a significance level of 0.05, confirms that the cohort has 80% power to show a significant difference”

SIXTEEN

It would be useful to see some mention of a statistical analysis plan given that results are presented also consider reporting incidence rates in the cohort and also some consideration as to how to treat true and apparent TRH as different groups.

-We have now inserted an additional paragraph in the methods section entitled-Statistics analysis plan -which addresses this issue:
The primary response is the probability of patients developing the outcome of interest as defined by Daugherty. A logistic regression model will be used to compare the probabilities between the two groups while adjusting for explanatory variables such as age, gender, socioeconomic status, baseline blood pressure, presence of diabetes or kidney disease as appropriate. Initially all explanatory variables will be included as adjusters and the ridge regression and the LASSO (Hastie et al, 2008) will be used to account for any multicollinearity present amongst the explanatory variables. Classification trees will be used to identify potentially useful interactions.


SEVENTEEN
Page 1 line 52-53 Please explain the sentence "it may reflect the phenotype of patients recruited within general practice....."

-This has been removed.

EIGHTEEN
Last page of discussion line 2-3- in the methods it appears to be stated that it was possible to delineate true vs apparent TRH. How will this study be able to accomplish this and why were others unable to as this is an important issue?

-See point TWO above.

NINETEEN
Lines 7-8 please explain your concerns with power given that you are not comparing outcomes to another group.

-See point FIFTEEN above.
Reviewer #2: Review of Paper

Wednesday, November 08, 2017

PAFS-D-17-00147

Prognosis of patients with apparent treatment resistant hypertension - A feasibility study Peter Hayes; Hannah Kielty; Monica Casey; Liam Glynn; Gerard J Molloy; Hannah Durand; John Newell; Andrew Murphy Pilot and Feasibility Studies

Summary: a well-written paper from authors who clearly have experience in pilot and practice-based studies. The quality of the paper is good and is appropriate for publication. Thank you

Abstract: The abstract covers the key areas in describing the study, without any need for corrections or changes;
-Thank you

Background; A succinct yet clear description of the background and need for this pilot study. No changes recommended;
-Thank you

Methods: The methods section covers the most salient topics and design components of this pilot study. In particular, I approve of the recruitment process, which endeavors to select patients/practices from various locations and background. The experience of the authors and the pre-tested research process comes through in the methods section, so many elements of the research process and research administration is implicit. The authors make is clear that the research process is driven and administered by research assistants, who coordinate the process.

TWENTY

However, a paragraph on how researchers and assistants would ensure or facilitate a smooth research process would be nice, alongside how participation in the research by GP practices was "incentivized".
"Tips for ensuring a smooth research process include pre-booking time slots for practice computers, showing flexibility regarding access times - multiple half days may be available as opposed to full days and administrator/front desk workload acknowledgement e.g. teas, courtesy and thank you cards. The signing of individual practice confidentiality agreements was also seen as important. These may not be required by local ethics committees, but GP’s data protection fears are eased by such. Tips for ensuring accurate data collection include ensuring the adequate training of researchers in use of the relevant patient’s data management system, and meeting with practice administrators prior to data collection. Administrators will know where specific data items are stored e.g. ABPM reports and how the files of those who are deceased or have moved on are managed in individual practices. These issues will need to be factored into future planning."

Regarding incentives, the following has been written in the Methods:

“There were no incentives provided to these practices to participate; however, a stipend of €1,000 was paid to all sixteen practices when assembling the initial cohort, as an acknowledgement for the extra workload involved.”

Regarding the facilitation of a smooth research process, the following has been written in the Discussion:

Results: A well-written section without any need for changes

TWENTY-ONE

Discussion & Conclusion: Some good insights and challenges are cited in this section related to a definitive study. An extra paragraph on how the research process was managed and some further recommendation on facilitating a smooth research process would be nice, especially around enticing GP practices to participate and any strategies used to facilitating data collection.

-See point TWENTY above.
TWENTY-TWO

Practice-based research is always tough to implement and any insights or advice to researchers related to how management and incentivizing participation in research by GP practices would be valuable.

-The following has been written in the Discussion:

“All practices that participated were part of a university affiliated research network WestREN. Regular e-mail updates and annual meetings where research projects were discussed are key to maintaining practice participation. Allowing practices to fulfil their mandatory audit commitments, whilst participating in research projects, is also welcome.”

Regarding incentivization, see point TWENTY above.

Figures and Tables: The tables are clear and the flow sheet offer a good description of patient flow in a CONSORT-like manner.

-Thank you

Reviewer #3:

The authors make a credible case for the merits of their proposed cohort study of patients with apparent Treatment Resistant Hypertension (aTRH) and, given the potential challenges in conducting such a study, it is also commendable that a feasibility study was carried out first.

TWENTY-THREE

While it is clear that they have conducted such a study to a high standard, they have not reported their experience in quite as much detail as might be helpful to other researchers.

-See point TWENTY above.
Firstly, though, there is some concern as to how representative their three 'pragmatically' chosen practices are of their entire cohort of 16 practices. Although chosen to get some geographical and practice size variation it seems they may not have captured variation that might be more relevant to the proposed major study such as variation in capacity for patient follow up and/or data gathering. The fact that only 5 patients of 210 were lost to follow up, exclusively through changing practice, and that the data collection on the remaining 205 appears to have been complete does seem rather atypical and unlikely to be sustained at quite that level in a larger study. Some more frank detail on how these practices were selected and some comment on whether or not they could truly be seen as typical would be useful. Even if they may not have data, some insights into whether or not they now feel the remaining practices might perform would be desirable.

-By comparing Tables 1 + 2, we have shown that the selected cohort (n=210) is matched in demographic and comorbidity to the entire cohort (n=646). We have no reason to think that these patients or their practices are atypical.

We have now written in the Methods section:

“For this feasibility study, three practices were pragmatically chosen from the original sixteen to reflect practice diversity – one was small and rural, one a medium and rural practice and one a large and mixed urban-rural practice. All sixteen practices used the same practice software system (Socrates®) to store patient data, were located within one hour’s travel of the university and had a mix of PCRS and private patients.”

Regarding follow-up, we note the older age and multi-morbidity of patients and the relatively smaller size of Irish practices as compared to the UK; all these factors may enhance patient follow-up. We have included the following section in the Discussion:

“The very low numbers lost to follow up and completeness of data are pleasing; however, this may not be replicated in the larger level and due allowance has been made in the power calculation.”
TWENTY-FIVE

The authors also state that the advantage of their scrutiny of individual records would be that it would provide insights into dosing, adherence and white coat hypertension. However, these issues, on which data ought to have been available from the feasibility study, are not reported on.

-See point TWO above.

TWENTY-SIX

They also say that the feasibility study would allow them to gain information on data collection time. Again, though, the data provided on this is limited to just total hours and average minutes per patient for data collection from records only. Some information on the total time required including time spent on practice engagement, travel etc. could be noted as well as, perhaps, some comment on time spend in training and setting up practices to make the kinds of detailed records for this kind of study should be included.

-The following is now reported in the Results:

“File search took place from June 19th to July 14th 2017 –a total of four weeks for three practices. The total time spent in data collection at the practices was 44 hours which was an average of 12.6 minutes per patient.”

TWENTY-SEVEN

Furthermore, as well as the average time per patient some indication of the range or variability of this time utilisation and some indication of whether this varied much between practices (and, if so, why) would also be useful.

-The following is now reported in the Discussion:

“The average research time of twelve minutes per patient includes data collection only, but travel to practices was a mean of 80 minutes return (maximum trip-two hour’s return). The main variation in data collection time between practices was the number of patient files examined. The main variation in data collection time between individual patients was the number of recorded health care interactions.”
Similarly, they claim that they have the advantage of having ABPM measurements which allows them to distinguish between what might be called 'true' Treatment Resistant Hypertension and 'apparent' Treatment Resistant Hypertension. However, no data on the proportion of these in their sample is recorded.

-This is now recorded in Tables 1 + 2.

I also note that cause of death was could not be determined from the clinical records for one patient and had to be obtained from the public record. Why was this? While this may seem to be only a minor issue involving only one case, if this were to be replicated across the larger cohort to a more significant level it have implications for the overall study as it might reflect serious gaps in records that would seriously undermine the goals of the larger study.

-We amended a paragraph in the Discussion as follows:

“Identification of cause of death from practice data also appeared straightforward with only one of six deaths requiring access to the on-line State Register. This was needed for an in-hospital patient death, where cause of death was unclear from practice clinical notes and notice of death, as opposed to cause of death, was recorded.”

Overall, therefore, this is a worthwhile study but I suspect, and would hope, that the authors have more insights into the issues likely to emerge in a larger study and more preliminary findings than they have reported here.

-See points TWO, FIFTEEN, TWENTY, TWENTY-TWO, TWENTY-FOUR, and TWENTY-SEVEN, above.