Reviewer 2 v.1

Comments to the Author

This is a retrospective review of the English NHS database regarding resource utilization for PAH patients. As this database is comprehensive for the entire country, this study overcomes some limitations of similar work done in countries such as the US, which is limited by a lack of a centralized database for healthcare utilization data. Data was collected from 4/1/2012 to 3/31/2018, a period of six years.

PH was defined based on ICD codes for PH, or the first of several events – RHC, use of PAH specific medication, or hospitalization event with referral. Followed until death or censor as last contact date or end of study date. The authors note the challenges inherent to the NES system regarding drug dispensation and classification of PAH, particularly as it relates to PDE-5i class medications. CTEPH was excluded. Length of hospitalization, inflation-adjusted costs, and incidence and prevalence were calculated.

2527 patients were included in the final data analysis. The majority were female and over 50, with substantial proportions of patients with cardiovascular comorbidities, comparable to more recent registry studies of PAH in other countries. The authors detail results regarding admissions, healthcare utilization costs, and stratify based on the top 20% of expenditure patients versus the full cohort. The authors conclude that there exist a sub-population of “high resource users” driving some of the trends seen in their data, and that healthcare utilization in PAH is substantial (although the authors do not contrast this with any non-PAH data in their study).

While the study in general is addressing a pertinent question in the field of PAH, I have a number of concerns regarding the methodology and approach.

Major Concerns:

1) The selection of the cohort is somewhat confusing. This is made even more confusing by the “cohort selection” section wording (page 4, line 44+), which details selection criteria in the absence of ICD coding, and figures 1 and 2. On the one hand, the wording and figure suggest patients can be either ICD classified, OR have one of the following: RHC, PAH drug, visit to specialty center (Page 4, line 21-33). On the other hand, the “cohort selection” section details multiple criteria to be met to be included in the study in the absence of an ICD-10 code, as detailed by the complex flowchart in Figure 2. By carefully looking through the Figure 2 flowchart, I gather the authors intended to combine ICD coding with additional criteria (RHC, PAH medication, specialty center referral), and to combine those metrics in a different way in the absence of ICD-10 coding, but this needs to be explained in a much clearer fashion, as it forms the basis of this paper’s study population. Only in the discussion is it apparent this is how the authors approached defining their cohort. I would also note that, by using Figure 2, a patient could have underlying scleroderma with digital ulcers, or an

underlying diagnosis of erectile dysfunction (both common enough in the PAH population), but be excluded from the study based on these diagnoses, so the algorithm used to identify patients in this cohort will inherently miss a significant subset of PAH patients (an issue the authors did, to their credit, discuss in the discussion section).

2) An additional limitation with the algorithm the authors utilize concerns patients with off-label therapy for PAH. For example, a patient with combined WHO-2 and WHO-3 disease could be provided with targeted therapy after a RHC, and be classified as "PAH" by the algorithm. Off-label PAH therapy for non-PAH patients with PH is a routine occurrence, indeed in the US other large studies have indicated that treatment is provided off-label routinely to WHO-2 and WHO-3 group PH patients, even without RHC, at between 40-80% in the US population. (Maron et al. Circulation 2019;139(16):1861-1864) The authors should address this potentially significant limitation in their discussion.

3) I am surprised the authors did not opt to compare the PAH patients to the "non-PAH" patients in terms of healthcare utilization and costs, particularly given that this algorithm for PAH patient selection is a different approach from other studies regarding healthcare utilization in the PAH population, and as such is not directly comparable to those studies. Additionally, the authors would have access to a substantial number of patients excluded from this cohort, and even simple descriptive statistics comparing included versus excluded patients would be informative and potentially enlightening. I would recommend the authors compare the PAH population to the non-PAH population to see if they are able to reach any conclusions regarding PAH patients as compared to non-PAH patients in terms of healthcare utilization

4) Use of the "one year after start of dataset" index to separate incident and prevalent patients doesn't make full sense. A patient could be newly diagnosed 2 months after start of the dataset, which would classify them as being "prevalent" by the criterion listed by the authors, even though this is a new diagnosis. This is further complicated by the classification algorithm used by the authors, which has multiple measures to classify disease, and as such is intended to identify "strict" PAH patients, but consequently is not as easy to use for something like incidence versus prevalence classification than a more binary tool like a date-associated ICD-10 code. I would remove this arbitrary classification scheme, and avoid referring to the "incident" versus "prevalent" patients in the results and analysis.

5) The authors note that the vast majority of outpatient visits lack an ICD-10 code to classify PAH-related from non-PAH related (Page 7, line 47-51). With that in mind, I do not see how these comparisons are made later in the manuscript (Table 2 describes outpatient visits stratified by PAH and non-PAH, but with only 10% of the data this would be misleading, a similar issue is seen in Table 4 and in Figure 5-B, Tables S2, S3, S6, and figures S-2 and S-3). Given the authors note this substantial limitation concerning outpatient visits in their data, I would not stratify the outpatient data into PAH and non-PAH.