HEALTH TECHNOLOGY APPRAISAL: NICE Health Technology Appraisal - Assessment Report Drugs for the treatment of Pulmonary Arterial Hypertension	
TO: NICE	**FROM: NHS Quality Improvement Scotland**

I have broken up my response into three sections. These sections as follows:-

1. Conclusions from the Assessment Report.
2. Concerns about the methodology of Assessment Report
3. Suggested additions or modifications that could be made before this Report goes before the appraisal committee

1. ***Conclusions from the Assessment report:***

- It appears that, although the report acknowledges the efficacy of directed pulmonary hypertension therapy when compared with supportive therapy (Digoxin, Diuretics, Warfarin etc), improvements with each of the three classes of drug (Prostanoids, PDE5 inhibitors and Endothelial Receptor Antagonists) are similar. Therefore, in the absence of comparative studies the choice of one or the other should be made on the basis of cost. (except presumably in Class IV patients where IV Epoprostenol is the only established treatment.
- Since it says intravenous Epoprostenol should only be used, for class IV patients then the cost analysis for class II/III patients will be between the Endothelial Receptor Antagonists, inhaled Iloprost or oral Sildenafil. The conclusion of the ACD draft appears to be that Sildenafil should be the favourite first choice monotherapy because of its relatively lower cost and, therefore, lower cost per QALY. I believe that for a number of reasons this analysis and the conclusions from this analysis are flawed.

2. ***Methodological concerns in the Assessment report***

- The methodology is flawed, and leads to the flawed conclusion that there are no data to suggest differences between therapies, that benefit is equal and thus cost is the only available discriminator.

- An assumption is made that mortality in standard care class 3 patients is 5% per 12 weeks without any deterioration to class 4, this suggests that many patients could die without the cost incurred during epoprostenol exposure, in clinical situations this would be extremely rare.

- It is assumed that no further improvement in functional class can occur after 12 weeks. In the case of disease modifying therapy (ERA) late improvement is not merely possible, but not uncommon and there is new data to support this.

- Just because the numbers of different types of pulmonary hypertension (idiopathic-PH, connective tissue associated-PH, congenital heart disease-PH etc) are relatively small, this is not a reason to lump these diseases together. They are very different and from a clinical point of view behave quite differently in terms of response to therapy. It is clear that some patients respond better to one of these three classes of technologies than the others. Thus for individual patients there are important differences in clinical outcomes. In part this is due to differences in the cause of PAH , very different outcomes in different sub groups of PAH (not considered in this report) and pathophysiology

- The data for Sildenafil used in the report assumed a dose of 20mgs tid whereas in the trial, the long term patients used 80mgs tid (but the drug is licensed only at 20 mgs tid).

- All studies were based on 12-16 week data. There was no placebo controlled long-term data in particular no long-term survival data and thus it really is impossible to claim utility of one drug over another in the long term. This data, , will be now available from the various registries in the UK and elsewhere and should be used.

- It is apparent that the assumptions inherent in a recurrent 12 week recycling of data over 30 years are incorrect, and that the assumptions with respect to mortality are highly speculative.

- Survival has been reported for Epoprostenol and bosentan at licensed doses but not for sildenafil, where data was gathered for 80 mg TDS rather than the licensed 20 mg TDS (these doses had statistically different haemodynamic effects). Functional class as an outcome is flawed for a number of reasons: firstly, the interpretation of functional class is very subjective. Secondly, there is blurring of the lines between functional class II & III. Thirdly, functional class change does not appear to agree with the much harder point of six-minute walk distance change. The rate of deterioration for any given functional class is assumed to be equal in all therapies, the data suggests otherwise:

    - 'Time to clinical worsening' has been a secondary endpoint for 12 double blind RCT for PAH and is likely to be more reliable than simple change in FC, Time to clinical worsening effectively identifies patients who deteriorate to class 4 or die. In the case of sildenafil and sitaxsentan there is no evidence to suggest that the rate of clinical worsening is reduced when compared to placebo but this has been shown with Bosentan .
    - The prescription of disease-targeted therapy for pulmonary arterial hypertension should be done only by the **nationally designated centres**. These centres have the expertise ,experience and technology to fully assess the patients and determine the best therapy for them or indeed whether therapy is appropriate at all. They are also better equipped to evaluate response to therapy. Currently all of the available PAH therapies are specific for PAH except for Sildenafil. his has had the consequence that Sildenafil has been used wildly outside the centres and patients have been wrongly placed on this drug and poorly followed up with disastrous clinical consequences and additional unjustified costs.
    - The number of patients who need specific therapy is very small in NHS terms**.** In Scotland 132 patients were on treatment on 31st July 2007. Even if

this number were to double or triple the number of patients would be very small.

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- It is not surprising that there have been differences, historically, in the chice of 1st line therapy for different patients eg a vasodilator response to NO would favour Sildenafil; patients with liver disease may not be ideal candidates for Bosentan; Sildenafil should be not used in patients with IHD particularly if taking NO donors; only Bosentan has been shown to be of clinical use in Congen HD and CTEPH

3. *Suggestive Modifications to the Assessment report*

- It should be stated that in the absence of head to head studies it is impossible to conclude that one monotherapy is better than the other and therefore all should be available to be tailored to individual patients.
- The authors should consider relatively new data showing changes in disease activity after 16 weeks which was not manifest prior to 16 weeks.
- The authors should consider using long term data available from the UK registries on the relative efficacy of drugs in particular on survival times.
- The authors should consider 'time to clinical worsening' rather than functional class as an end point as this is much more likely to be reliable.
- The authors should state that these drugs should all be prescribed by the designated centres to ensure they are used appropriately. This should decrease the overall cost.
- The authors should consider suggesting a head-to-head comparison between therapies, which could be funded by NHS R&D.
- The authors should consider long-term data on the different sub groups of pulmonary hypertension ie connective tissue disease, assertive pulmonary hypertension,idiopathic pulmonary hypertension and inoperable thromboembolic pulmonary hypertension (treated by drugs) as well as congenital heart disease. The outlook in the different groups is quite different and it is likely that the response to therapies is also quite different particularly in Congenital Heart disease and CTEPH

[redacted], 25 September 2007