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Dear Ms Bemrose

Re: NICE Draft Pulmonary Arterial Hypertension Report: "Clinical and cost effectiveness of treatments for pulmonary arterial hypertension (PAH) within their licensed indications"

The Royal College of Physicians is grateful for the opportunity to respond to this consultation. In so doing, we wish to make the following comments:

This analysis focuses on the data available from 12 to 16 week randomised clinical trials in patients with predominantly idiopathic PAH and PAH associated with connective tissue disease. The majority of patients will live longer than this and the number of patients treated in England is small. Our response highlights three important concerns:

1. The data are hard won, originate largely from pharmaceutical sponsored studies and fall short of robust survival figures. The exception is epoprostenol. Epoprostenol is the only therapy that has been shown to prolong life in PAH and there is universal consensus on its value as a rescue therapy for patients presenting severely ill with PAH. The use of this drug is complicated by its kinetics and pharmacology and demands specialist advice. Transferring patients from epoprostenol to other therapies is particularly challenging. **It is essential that Epoprostenol is retained as a therapeutic option for PAH for specialists that are skilled in its use.**

2. A comparison of licensed therapies based on cost has merit but there are limitations imposed by the available data. There is a notable lack of head to head studies and the heterogeneous nature of the disease within and between different subclasses of PAH makes comparisons across studies difficult. There is little doubt that all the licensed drugs improve patients' symptoms in the short term but extrapolation based on 16 week data is unscientific. **The report should state that in the absence of head to head studies it is impossible to conclude that one monotherapy is better than another on any grounds.**

3. While placebo-controlled survival data are lacking for all treatments except epoprostenol, there is more experience with some treatments such as bosentan and iloprost, than sildenafil. That experience (contained in registry data compiled from real-life practice) is in keeping with the claim that the rate of progression of the disease is retarded by these therapies. This data

cannot be dismissed. Neither can retardation of disease progression be assumed to apply to sildenafil. The latter may have a greater effect on the systemic circulation than endothelin receptor antagonists (witnessed by systemic hypotensive episodes) and also the heart (where recent data indicate its target –PDE5 - is expressed in the diseased hypertrophied right ventricle). Therefore sildenafil may be apparently the most cost-effective in the short-term but the data are not there to allow a confident prediction that this is maintained over a year (particularly with the licensed dose of sildenafil, 20mg TID). **It must be considered a serious omission that survival data where published for the therapies at their licensed doses have been ignored.**

In responding to this consultation, we have also seen the response submitted by the British Society of Rheumatology and would like to further endorse those comments.

Yours sincerely