[Jonathan.minton@glasgow.ac.uk](mailto:Jonathan.minton@glasgow.ac.uk) 29 October 2013

Dear Sir/Madam

**Re: Manuscript: “When is it cost effective to use transthoracic echocardiography (TTE) to aid the decision to prescribe oral anticoagulants (OACs) in patients with newly diagnosed atrial fibrillation (AF)? An economic evaluation“**

Please find enclosed our above-titled manuscript, which presents an economic evaluation of a health technology. This manuscript makes a valuable contribution to the scientific literature in the following ways:

* **Model sophistication**: We use a discrete event simulation (DES) modelling approach to estimate the cost and clinical consequences of using a diagnostic technology to make an important clinical decision. The right clinical decision depends on patient history, and changes over time as the patient history changes. Most economic evaluations use cohort level Markov models, which do not allow individual patient histories and treatments to be tracked in this way. Our DES modelling approach does.
* **Downstream and upstream consequences**: To estimate the cost effectiveness of using TTE in guiding the management of AF patients, the downstream consequences of different types of correct and incorrect decisions need to be estimated. Our model does this, by simulating the patient histories of patients from time of assessment, with or without TTE, until death. Different treatment options following diagnosis (see below) imply different downstream consequences, and so the treatment options have an upstream effect on the cost-effectiveness of our use of TTE. Our model provides data driven estimates of these complex upstream and downstream effects.
* **Comparison between OACs**: In addition to warfarin, the implications of using the newer OACs dabigatran and rivaroxaban are also simulated in our model. These newer OACs have different costs, efficacy and risk profiles to warfarin and each other, meaning the clinical tipping points – when benefit outweighs harm – are also different. In addition to these differences affecting when it is cost effective to use TTE as a decision aid – the upstream consequences as described above – our simulations also allow, perhaps for the first time, the clinical and cost effectiveness of the OACs to be compared with each other. Although not the focus of our paper, these are compared in full incremental analyses in the appendix.

We think Jeremy D Goldhaber-Fiebert, John William Stevens, Yiru Guo, Weiqing Han, Jeroen Hendrikse, Sam Eldabe, Talitha L Feestra, and David W Dowdy would be appropriate choices of academic editor for our submission. Regarding reviewers with expertise in the clinical aspects of our manuscript, we recommend Prof Lalit Kalra, Dr Andreas Wolff, and Dr Matthew Fay. Regarding reviewers with expertise in health economic evaluation, we would recommend Dr Praveen Thokala, Prof Steve Palmer, Prof Elisabeth Fenwick, Dr Pelham Barton, Stephen Rice and Micah Rose.

I have not had any prior interactions with PLOS regarding this manuscript and look forward to your response to this submission.

Yours sincerely,

Dr Jon Minton