Appendix 2 SAMPLE Protocol amendments

Protocol v2 13.08.12

1. Secondary Endpoints
   We have set out the ‘Quality of Life’ endpoint to make clear that it is a distinct endpoint.

2. Data Safety Monitoring Committee
   The New Zealand (NZ) Ethics Committee requires all clinical trials to have a Data Safety Monitoring Committee (DSMC). Although this trial is comparing two standard clinical practices for the management of malignant pleural effusion, the use of indwelling pleural catheters (IPC) is quite novel for NZ. Following discussion with the Trial Steering Committee we have decided to convene a DSMC the details of which are entered into the protocol.

3. Trial Flowchart
   So as not to be proscriptive to clinicians in the size of chest drain used we have now provided a range of size 12 to size 18F. The Steering Committee also felt that this would avoid external reviewer criticism and provide some standardisation of the pleurodesis arm of the trial.

Protocol v3 18.09.12

1. Trial Committees and Adverse Event Management
   We have further clarified the role of the DSMB with regards to Serious Adverse Events.

2. Adverse Events
   This trial is recruiting participants who have life-limiting malignant disease and a percentage of these participants are anticipated to die due to disease progression during their time in the trial. Following discussion with the Steering Committee and with the SCGH Department of Research we have modified the protocol so that we will not report these anticipated deaths as Serious Adverse Events.

Protocol v4 16.09.13

1. Changes to Randomisation Stratification
   With the addition of the National University of Singapore, under PI: Dr Pyng Lee, as a site and following extensive discussions with our independent Trial Steering Committee (TSC), it has been decided to alter the randomisation stratification. This is to minimise for the potential differences in length of hospital stay / admission threshold to accommodate clinical practice in Singapore.

   The current stratification is for mesothelioma and trapped lung. Singapore vs the rest of the study sites will be added as a third stratification. Although we have recruited 40% of our target figure we do not believe that this change will alter the study results.

   To maintain allocation concealment, randomisation was performed in real time by a web interface (Filemaker Server Advanced, Filemaker Inc., Santa Clara). Initially, a
minimisation program was used so that patients within Australia and New Zealand (Australasia) were allocated with a probability of 0.5-0.7 favouring the treatment that would minimise differences between groups on two key prognostic factors (mesothelioma and trapped lung). When Singapore was added as a site in late 2013, stratification by region (Australasia versus Singapore) was added because of differences in baseline characteristics (predominantly the prevalence of mesothelioma) between Australasia and Asia. The probability favouring the treatment that would minimise bias was increased to 0.8 accordingly to compensate for this added variable (1).