Issue 1 Adjustment for patients who died in PFS on the calculation of post-progression survival

Description of problem	**Description of proposed amendment**	**Result of amended model or expected impact on the result (if applicable)**
In the ACD section 4.2.15, it is explained that in the AG model, "the estimate for overall survival was obtained by combining estimates of mean progression-free survival and mean post-progression survival in each group, and adjusting for the patients who died at or before progression (5.8% in the anastrozole alone group and 9.3% in the trastuzumab plus anastrozole group)". In the TAnDEM trial, 6 patients in each treatment arm died at or before disease progression. Given that there were 103 patients in the intervention arm and 104 patients in the control arm, it would appear that the anastrozole figure was calculated correctly (5.8%) but the proportion in the trastuzumab arm has been overestimated (97/103 = 5.8%).	On Sheet TA_AI, cell AO41, which we believe is incorrectly labeled ''Progressed AI only patients" (as this refers to the trastuzumab arm, it should probably read "Progressed TR+AI patients", the current value is 93. This value should be 97 if the intent is to reflect the number of patient who did not die before or during disease progression (i.e. 103 patients started the trial and 6 of these patients died).	When changing the incorrect cell within the AG model (Sheet TA_AI, cell AO41), this results in a decrease to the ICER (**from £73,135 to £69,514**) resulting from an improved mean time in PPS determined from the trastuzumab arm.

Issue 2 Calculation of Progression-Free Survival and the associated trastuzumab costs

Description of problem	Description of proposed amendment	Result of amended model or expected impact on the result (if applicable)
The methods used in deriving the PFS Weibull curve were not clearly presented and it is unclear as to whether estimates of uncertainty around their parameter estimates were incorporated into the PSA performed. From comparison of the Roche and AG models, it is clear that the estimate of time in PFS differs considerably between the Roche original model (1.19 years) and the assessment group's model (1.30 years). In the Roche model, we have utilized the Kaplan Meier PFS curves for both the trastuzumab arm and anastrozole arm from the TAnDEM trial. This data was complete (i.e. no patients remained in PFS at the end of follow-up) and therefore no extrapolation was conducted. It can be considered that the mean time in PFS presented in our model reflects the mean time observed in the clinical trial.	Utilise the KM curves to determine the time in PFS and the Roche methodology for utilising actual individual patient weights from the clinical trial to determine the required number of vials of trastuzumab. The impact of this potential overestimation of time in PFS in the AG model will affect multiple parameters in the model, but the most considerable impact of this overestimate as it relates to the ICER will likely be the overestimation of the cost of trastuzumab and anastrozole combination therapy which is given until disease progression. The cost of the trastuzumab and anastrozole combination therapy is estimated to be approximately £6,500 greater in the AG model (£31,272) compared to the Roche model (£24,774).	In order to provide a crude calculation of the impact of potentially overestimating average time in PFS and therefore overestimating the cost of trastuzumab by £6,500, we have removed an additional £6,500 from the numerator of the AG modified ICER, resulting in a downwards shift of the ICER **from £69,514 to £57,591**.