# Supplementary file 2

***Sensitivity analyses***

Sensitivity analyses explored the impact on results of varying key assumptions made in the base case for primary and secondary analyses: including accommodation of participants in domestic as well as residential care in total health and social care costs; examining total (EQ-5D-5L) QALY and costs for the dyad (person with dementia and unpaid carer); and using an alternative valuation and definition of unpaid carer time. Accommodation costs of domestic residence were sourced from UK Household expenditure statistics (Office for National Statistics, 2018) and ‘sheltered’ domestic housing from Curtis and Burns (2017). Unpaid carer time was valued at replacement cost, using the hourly cost of a home care worker. This valuation was also used to calculate unpaid care time defined as the hours of the day that the person with dementia could not be left alone by the carer.

In addition, we explored the impact on results of varying the modelling approach in the primary cost-effectiveness analyses. First, we included a covariate for gender in the multilevel model to adjust for a baseline imbalance between groups. Second, as an alternative approach to the MLM and to address skewness typical of cost data, we applied seemingly-unrelated regressions (Willan *et al.*, 2004) (where cost and outcome equations were the same as in the MLM) to 4,000 replicates generated by a two-stage bootstrapping procedure suitable for clustered data as described by Gomes *et al.* (2012). This analysis was conducted in R (R Core Team, 2020).

***Sensitivity analyses***

Mean costs used in sensitivity analyses are reported in Table S2.1 and results of sensitivity analyses of the primary outcome are displayed in Table S2.2. Results of analysis of CMAI scores and health and social care costs that included the costs of domestic accommodation were similar to the base case results, with no significant differences between groups. The cost per 6-point difference was slightly lower than in the primary analysis but unbounded as in the base case results. Analyses adjusting for the baseline imbalance between groups in proportion of female participants yielded similar results to the base case, with an unbounded ICER. Results of a SUR model applied to samples from a two-stage bootstrapping routine indicated no differences between groups in costs or CMAI scores; model estimates produced a small positive unbounded ICER of £136 per 6-point difference.

In terms of secondary outcomes, analyses explored the impact on results for EQ-5D-5L QALY and societal costs of valuing unpaid carer time at replacement cost, alone and in combination with an alternative method of estimating hours of unpaid carer time (Table S2.3). The societal costs were significantly greater in the mirtazapine group if valuing unpaid carer time at replacement cost. Valuation at replacement cost resulted in a negative NMB at £20,000 with negative upper and lower confidence limits (the costs outweighed the benefit of the intervention). Using an alternative calculation of unpaid carer hours increased the cost of both groups (doubling it in the placebo group) but the groups did not differ. Valuation of the alternative estimation of unpaid care time at replacement cost resulted in an unbounded ICER and negative NMB at £20,000 with confidence intervals crossing zero.

Examining combined QALY and health and social care costs of participant and dyadic carer, the groups did not differ. The ICER was unbounded and had a negative sign because the mirtazapine group had slightly lower QALY and slightly higher costs.

References:

**Curtis, L. and Burns, A.** (2017). *Unit Costs of Health and Social Care 2017*. Canterbury: Personal Social Services Research Unit, University of Kent.

**Gomes, M., Grieve, R., Nixon, R., Ng, E. S., Carpenter, J. and Thompson, S. G.** (2012). Methods for covariate adjustment in cost-effectiveness analysis that use cluster randomised trials. *Health Economics*, 21, 1101-1118.

**Office for National Statistics** (2018). Household expenditure by economic activity status of the household reference person, UK. Financial year ending 2017. Table A17. London: Office for National Statistics,.

**R Core Team** (2020). R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing.

**Willan, A., Briggs, A. and Hoch, J.** (2004). Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectivenessdata. *Health Economics*, 13, 461 - 475.

Table S2.1. Sensitivity analyses of mean costs (standard errors), at baseline, weeks 6 and 12 assessments (£, 2016-17)

|  |  |  |  |
| --- | --- | --- | --- |
| **Cost categories** | **Mirtazapine** | **Placebo** | **Mirtazapine-Placebo difference** |
|  | **N** | **Mean** | **SE** | **N** | **Mean** | **SE** | **Mean**  | **95% CI** |
| **Baseline (prior 12 weeks)** |  |  |  |  |
| Accommodation costs |  |  |  |  |  |  |  |  |
| domestic residence (includes sheltered) | 100 | 1 596 | 146 | 101 | 1 662 | 144 | -66 | -469, 338 |
| permanent residence | 100 | 5 447 | 308 | 101 | 5 555 | 345 | -108 | -1 020, 804 |
| Total accommodation, health and social care inc. med | 93 | 7 136 | 403 | 99 | 7 112 | 422 | 24 | -1 130, 1 178 |
|  | **Expected=63** |  | **Expected=68** |  |  |  |
| Total societal, replacement cost | 53 | 29 461 | 2 002 | 65 | 27 514 | 2 076 | 1 947 | -3 847, 7 740 |
| Total societal, alternative care time  | 49 | 50 224 | 1 488 | 58 | 51 220 | 1 466 | -995 | -5 162, 3 171 |
| **Week 6 (prior 6 weeks)** |  |  |  |  |
| Accommodation costs |  |  |  |  |  |  |  |  |
| domestic residence (includes sheltered) | 85 | 771 | 79 | 91 | 769 | 77 | 2 | -215, 219 |
|  of permanent residence | 85 | 2 739 | 162 | 91 | 2 966 | 192 | -227 | -726, 273 |
| Total accommodation, health and social care inc. med | 83 | 3 294 | 160 | 89 | 3 797 | 242 | -503 | -1 084, 79 |
|  | **Expected=53** |  | **Expected=60** |  |  |  |
| Total societal, replacement cost | 48 | 15 774 | 1 008 | 55 | 12 899 | 1 027 | 2 875\* | 3, 5748 |
| Total societal, alternative care time | 45 | 26 039 | 475 | 50 | 25 364 | 952 | 67 5 | -1 510, 2 860 |
| **Week 12 (prior 6 weeks)** |  |  |  |  |
| Accommodation costs |  |  |  |  |  |  |  |  |
| domestic residence (includes sheltered) | 78 | 731 | 83 | 86 | 756 | 79 | -25 | -251, 201 |
|  permanent residence | 78 | 2 862 | 180 | 86 | 3 032 | 200 | -170 | -705, 365 |
| Total accommodation, health and social care inc. med | 77 | 3 794 | 267 | 85 | 3 643 | 220 | 151  | -527, 830 |
|  | **Expected=49** |  |  **Expected=56** |  |  |  |
| Total societal, replacement cost | 44 | 16 078 | 1 125 | 51 | 12 415 | 1 008 | 3 663\* | 671, 6654 |
| Total societal, alternative care time measure | 40 | 26 754 | 742 | 47 | 25 026 | 963 | 1 728 | -754, 4211 |

\*p<0.05

Table S2.2. Sensitivity analyses of primary participant outcomes and costs over 12-week study follow-up, raw and adjusted difference between groups and incremental cost-effectiveness ratios

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Outcomes****& Costs** | **Mirtazapine** | **Placebo** |  | **Mirtazapine-****Placebo difference** |  |  |  |  | **Cost per** **6-point difference2** |
|  | **Mean** | **(SE)** | **Mean** | **(SE)** |  | **Mean (95% CI)** |  | **Adjusted (95% CI)** | **p1** |  | **C/E** |
| *CMAI - participant* |  |  |  |  |  |  |  |  |  |  |  |
| *Total HSC costs including**domestic accommodation* |  |  |  |  |  |  |  |  |  |  |  |
| Observations  | N=72 | N=79 |  |  |  |  |  |  |  |
| CMAI | 61.847 (2.659) | 60.848 (2.490) |  | 0.999 (-6.193, 8.191) |  | -2.506 (-8.299, 3.287) | 0.396 |  | -212/0.418=-507 |
| Total costs | 7 234 (390) | 7 380 (462) |  | -146 (-1 353, 1 060) |  | -212 (-1 375, 951) | 0.721 |  |
| *Statistical model adding* *sex as covariate* |  |  |  |  |  |  |  |  |  |  |  |
| Observations  | N=72 | N=79 |  |  |  |  |  |  |  |
| CMAI | 61.847 (2.659) | 60.848 (2.49) |  | 0.999 (-6.193, 8.191) |  | -1.726 (-7.613, 4.162) | 0.566 |  | -278/0.288=-956 |
| Total HSC costs  | 5 752 (513) | 5 877 (591) |  | -125 (-1 686, 1 435) |  | -275 (-1 756, 1 206) | 0.716 |  |
| *Alternative statistical model3* |  |  |  |  |  |  |  |  |  |  |  |
| Observations  | N=72 | N=79 |  |  |  |  |  |  |  |
| CMAI | 61.847 (2.659) | 60.848 (2.49) |  | 0.999 (-6.193, 8.191) |  | -2.253 (-9.847, 7.794) | 0.453 |  | 51/0.376=136 |
| Total HSC costs  | 5 752 (513) | 5 877 (591) |  | -125 (-1 686, 1 435) |  | 51 (-1 304,1 432) | 0.900 |  |  |

1. p-value of the adjusted difference

2. Reversed so that a higher score indicates less agitation and a lower score indicates more agitation

3. Seemingly unrelated regression; adjusted difference estimate is presented with bias corrected and accelerated 95% confidence intervals generated from 4000 replications of 2-stage bootstrap

Table S2.3. Sensitivity analyses of secondary participant outcomes and costs over 12-week study follow-up, raw and adjusted difference between groups and incremental cost-effectiveness ratios

| **Outcomes****& Costs** | **Mirtazapine** | **Placebo** |  | **Mirtazapine-****Placebo difference** |  |  | **ICER** | **NMB at** **£20,000** | **NMB at** **£30,000** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Mean** | **(SE)** | **Mean** | **(SE)** |  | **Mean** **(95% CI)** |  | **Adjusted** **(95% CI)** | **p1** |  | **C/E** | **Mean** **(95% CI)** | **Mean** **(95% CI)** |
| *Societal* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Replacement cost2  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Observations  | N=38 |  | N=45 |  |  |  |  |  |  |  |  |  |  |
| QALY-EQ-5D-5L | 0.125 (0.009) | 0.147 (0.007) |  | -0.022 (-0.045, 0.001) |  | -1.813 (-8.426, 4.799) | 0.589 |  | -3 366 204 | -8 169 (-14 178, -2 160) | -8 193 (-14 189, -2 197) |
| Total costs  | 33 090 (2 246) | 24 966 (2 105) |  | 8 125\* (1 989, 14 260) |  | 7263 (1 328, 13 197) | 0.017 |  |  |  |  |
| *Societal* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Replacement cost2 + alternative unpaid care est. |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Observations  | N=35 |  | N=39 |  |  |  |  |  |  |  |  |  |  |
| QALY-EQ-5D-5L | 0.129 (0.010) | 0.150 (0.008) |  | -0.022 (-0.046, 0.003) |  | -2.291 (-9.273, 4.691) | 0.518 |  | -842 854 | -3 730 (-8 173, 712) | -3 774 (-8 230, 682) |
| Total costs | 53 241 (1 145) | 49 685 (1 887) |  | 3 556  (-966, 8 079) |  | 3 242 (-1 114, 7 597) | 0.143 |  |  |  |  |
| *QALY – Participant & carer* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| *HSC* |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Observations  | N=40 |  | N=44 |  |  |  |  |  |  |  |  |  |  |
| QALY-EQ-5D-5L | 0.311 (0.010) | 0.336 (0.009) |  | -0.025 (-0.051,0.001) |  | 0.000(-0.014, 0.014) | 0.988 |  | -4 439 387 | -465 (-2 242, 1 312) | -466 (-2 241, 1 310) |
| Total costs  | 3 291 (632) | 2 987 (696) |  | 303 (-1 580, 2 187) |  | 463 (-1 362, 2 288) | 0.617 |  |  |  |  |

1. p-value of the adjusted difference

2. Replacement cost of unpaid care

\*p<0.05