# SUPPLEMENTARY MATERIAL

Long-term effectiveness of cognitive therapy for refractory social anxiety disorder
: one-year follow-up of randomised controlled trial

## Contents

## Supplementary Results:

**Supplementary Table 1.** Observed short-term raw outcome data in both groups

| | | Adjunctive CT | | UC alone | | Group effect | *p* value |
|---|---|---|---|---|---|---|---|
| | | **Mean** | **(*SD*)** | **Mean** | **(*SD*)** | | |
| **LSAS-SR (primary)** | Week 0 (Pre) | 81.38 | (22.14) | 83.29 | (16.60) | $F(1, 40)=0.10$ | 0.754 |
| | Week 8 (Mid) | 63.81 | (16.09) | 81.10 | (22.84) | $F(1, 38)=11.71$ | 0.001 |
| | Week 16 (Post) | 39.48 | (21.74) | 82.40 | (20.69) | $F(1, 38)=55.74$ | <0.001 |
| **PHQ-9** | Week 0 (Pre) | 10.57 | (5.55) | 9.76 | (5.22) | $F(1, 40)=0.24$ | 0.629 |
| | Week 8 (Mid) | 8.43 | (4.44) | 9.20 | (5.26) | $F(1, 38)=1.49$ | 0.230 |
| | Week 16 (Post) | 6.81 | (5.49) | 10.50 | (5.62) | $F(1, 38)=7.75$ | 0.008 |
| **GAD-7** | Week 0 (Pre) | 9.76 | (5.34) | 7.52 | (5.16) | $F(1, 40)=1.91$ | 0.175 |
| | Week 8 (Mid) | 6.62 | (4.43) | 7.70 | (5.33) | $F(1, 38)=4.26$ | 0.046 |
| | Week 16 (Post) | 5.33 | (5.67) | 9.05 | (4.82) | $F(1, 38)=11.15$ | 0.002 |
| **EQ-5D** | Week 0 (Pre) | 0.65 | (0.10) | 0.71 | (0.11) | $F(1, 40)=2.93$ | 0.095 |
| | Week 8 (Mid) | 0.73 | (0.19) | 0.72 | (0.14) | $F(1, 38)=0.78$ | 0.383 |
| | Week 16 (Post) | 0.82 | (0.24) | 0.72 | (0.13) | $F(1, 38)=5.39$ | 0.026 |

Note: Between-group analyses for week 0 were conducted using ANOVA. For weeks 8 and 16, ANCOVA was used, controlling for baseline score. Higher scores on the EQ-5D indicate better QOL. Higher scores on other measures indicate greater pathology or severity.

**Supplementary Table 2.** Observed long-term raw outcome data in the adjunctive CT group

| | | Adjunctive CT | | Significant pairwise comparisons (time) |
|---|---|---|---|---|
| | | Mean | (*SD*) | |
| **LSAS-SR (primary)** | Week 0 (Pre) | 81.38 | (22.14) | |
| | Week 8 (Mid) | 63.81 | (16.09) † | |
| | Week 16 (Post) | 39.48 | (21.74) † | |
| | Week 20 (1M-FU) | 38.67 | (21.00) † | Pre > Post > 1Y-FU |
| | Week 28 (3M-FU) | 39.08 | (31.06) † | |
| | Week 40 (6M-FU) | 35.31 | (25.36) † | |
| | Week 64 (1Y-FU) | 30.28 | (15.72) ‡ | |
| **PHQ-9** | Week 0 (Pre) | 10.57 | (5.55) | |
| | Week 8 (Mid) | 8.43 | (4.44) | |
| | Week 16 (Post) | 6.81 | (5.49) † | |
| | Week 20 (1M-FU) | 6.33 | (6.52) † | Pre > Post > 1Y-FU |
| | Week 28 (3M-FU) | 6.60 | (7.63) † | |
| | Week 40 (6M-FU) | 5.54 | (6.74) † | |
| | Week 64 (1Y-FU) | 3.94 | (3.09) ‡ | |
| **GAD-7** | Week 0 (Pre) | 9.76 | (5.34) | |
| | Week 8 (Mid) | 6.62 | (4.43) † | |
| | Week 16 (Post) | 5.33 | (5.67) † | |
| | Week 20 (1M-FU) | 5.07 | (5.68) † | Pre > Post = 1Y-FU |
| | Week 28 (3M-FU) | 6.20 | (6.63) † | |
| | Week 40 (6M-FU) | 5.46 | (5.11) † | |
| | Week 64 (1Y-FU) | 3.59 | (3.50) † | |
| **EQ-5D** | Week 0 (Pre) | 0.65 | (0.10) | |
| | Week 8 (Mid) | 0.73 | (0.19) | |
| | Week 16 (Post) | 0.82 | (0.24) † | |
| | Week 20 (1M-FU) | 0.81 | (0.17) † | Pre > Post = 1Y-FU |
| | Week 28 (3M-FU) | 0.79 | (0.20) † | |
| | Week 40 (6M-FU) | 0.85 | (0.13) † | |
| | Week 64 (1Y-FU) | 0.87 | (0.14) † | |

† $p < 0.05$ significant difference in pairwise comparisons with week 0.

‡ $p < 0.05$ significant difference in pairwise comparisons with both weeks 0 and 16.

Note: Higher scores on the EQ-5D indicate better QOL. Higher scores on other measures indicate greater pathology or severity.

**Supplementary Table 3.** Number of patients who reached response and remission criteria

| | Adjunctive CT (*n* = 21) | | UC alone (*n* = 21) | |
|---|---|---|---|---|
| | **Responded** | **Remitted** | **Responded** | **Remitted** |
| **Week 16 (Post)** | 18 / 21 | 9 / 21 | 1 / 20 | 0 / 20 |
| **Week 64 (1Y-FU)** | 18 / 18 | 12 / 18 | N/A | N/A |

Note: One patient in the UC alone group dropped out before week 16, and three patients in the adjunctive CT group dropped out before week 64. Treatment response was defined as a 31% or greater reduction in the total LSAS-SR score. Remission was defined as a final LSAS-SR score of 36 or less and no longer meeting the diagnostic criteria for SAD.

**Supplementary Appendix.** Cost-effectiveness of adding CT to usual care

We additionally evaluated the cost-effectiveness of individual CT as an adjunct to usual care for antidepressant-refractory SAD, from the public healthcare payer's perspective. As described in the main paper, data were collected for both groups for 16 weeks, but we did not obtain one-year follow-up data in the UC alone group (only in the adjunctive CT group).

For the economic analysis, utility measure was based on health-related quality of life, determined using the EQ-5D. EQ-5D scores were converted into utility values based on an algorithm for the Japanese population [1]. Based on these scores, Quality-Adjusted Life-Years (QALYs) were calculated using the time-weighted average of the utility values.

Direct costs incurred for the provision of individual CT were based on the FY2016 health insurance scheme in Japan. In this scheme, the cost for each CT session is divided into three types: "CBT-1" (5,000 JPY), provided by a designated psychiatrist (Mental Health and Welfare Law-authorised) cooperating with psychiatric emergency medical services; "CBT-2" (4,200 JPY), provided by a medical doctor who does not meet the CBT-1 criteria; and "CBT-3" (3,500 JPY), provided by a registered nurse. For the primary approach (Approach 1), the cost for each CT session was presumed to be based on the FY2016 scheme. If a CT session was provided by a psychologist or a psychiatric social worker (not covered by the insurance), we assumed a paramedical expense of "CBT-3". For scenario approaches, we assumed that all CT sessions were provided at the highest expense in Japan ("CBT-1") (Approach 2), and that all CT sessions were provided at the same expense as typical face-to-face CBT in the UK (Approach 3) [2]. Table 1 shows presumed unit cost of CT for each approach. We did not consider the direct costs of usual care provided by primary psychiatrists as we did not collect data regarding the use and cost of care and medication for either of the groups after the short-term intervention period was concluded. No significant differences were noted between the groups in antidepressant or anxiolytic doses over 16 weeks (see online Supplementary Table 1 in the previous trial [3]). The indirect costs (e.g. loss of patient's productivity) and educational costs for CT therapists were not included in the public healthcare payer's cost measures.

**Table 1.** Presumed unit cost of CT for each approach

| Approach | Presumed location and provider to calculate unit cost of CT | Cost per session (JPY) |
|---|---|---|
| **1 (Primary)** | Japan, face-to-face CBT by a designated psychiatrist (CBT-1) | 5,000 |
| | Japan, face-to-face CBT by a registered nurse (CBT-3) | 3,500 |
| **2 (Scenario)** | Japan, face-to-face CBT by a designated psychiatrist (CBT-1) | 5,000 |
| **3 (Scenario)** | UK, typical face-to-face CT/CBT | 14,550 |

*Note: The national health insurance scheme in Japan uses the more general term, CBT (cognitive behavioural therapy), when calculating unit cost of CT.*

The key outcome of the economic analysis is the incremental cost-effectiveness ratio (ICER), a ratio of the difference in incremental costs and the difference in incremental QALYs between groups. As stated, incremental costs only occurred for the provision of individual CT in the adjunctive CT group. Due to a lack of follow-up data for the UC alone group, reflected in non-significant improvements observed during the 16-week short-term intervention period (Supplementary Table 1), the QALYs in week 16 for the UC alone group were assumed to be stable until the end of the follow-up period. If the ICER for adjunctive CT is below the predetermined threshold of willingness-to-pay for additional QALY among Japanese (5 million JPY) [4], adjunctive CT for refractory SAD is considered cost-effective.

The robustness of the results in the primary economic analysis (Approach 1) was tested using multiple one-way sensitivity analyses to investigate sensitivity of ICERs to changes in key parameters, costs of CT (by paramedical staff/designated psychiatrist) and differences in QALYs between groups, varying each parameter by plus/minus 20%.

Table 1 shows incremental costs and QALYs, as well as the ICER in each approach. In the primary economic analysis (Approach 1), most CT sessions (95.9%) were provided by paramedical staff (cost per session at approximately 3,500 JPY), with a total incremental cost of 1,122,000 JPY and a QALY of 1.19567. Thus, the ICER for Approach 1 was calculated as 938,386 JPY, which is below the accepted cost-effective threshold of 5 million JPY, indicating that adjunctive CT for refractory SAD is a cost-effective treatment. In Approach 2, where all sessions were assumed to be provided by a designated psychiatrist (cost per session of 5,000 JPY), the ICER was 1,317,253 JPY. Total incremental cost was the highest in Approach 3, where typical face-to-face CBT expense in the UK was applied to all sessions (cost per session of 14,550 JPY), and the ICER was 3,833,206 JPY. Even if we estimate the 20% higher cost in Approach 3, the ICER was 4,599,848 JPY, which is still below the accepted cost-effective threshold.

**Table 2.** Incremental cost and QALY, and ICER for each approach

| Approach | Incremental cost (JPY) | Incremental QALY | ICER (cost/QALY) | ICER (20% lower) | ICER (20% higher) |
|---|---|---|---|---|---|
| **1 (Primary)** | 1,122,000 | 1.19567 | 938,386 | 750,709 | 1,126,063 |
| **2 (Scenario)** | 1,575,000 | 1.19567 | 1,317,253 | 1,053,802 | 1,580,704 |
| **3 (Scenario)** | 4,583,250 | 1.19567 | 3,833,206 | 3,066,565 | 4,599,848 |

*Note: Accepted cost-effective threshold of the ICER is 5 million JPY*

Figure 1 demonstrates the impact on the ICER for the primary economic analysis (Approach 1) when varying parameters singly using a one-way sensitivity analysis. Differences in QALYs between groups was the most sensitive parameter, but the ICER for all parameters analysed remained below the cost-effective threshold of 5 million JPY. This finding demonstrated that the Approach 1 analysis was still robust under different assumptions.

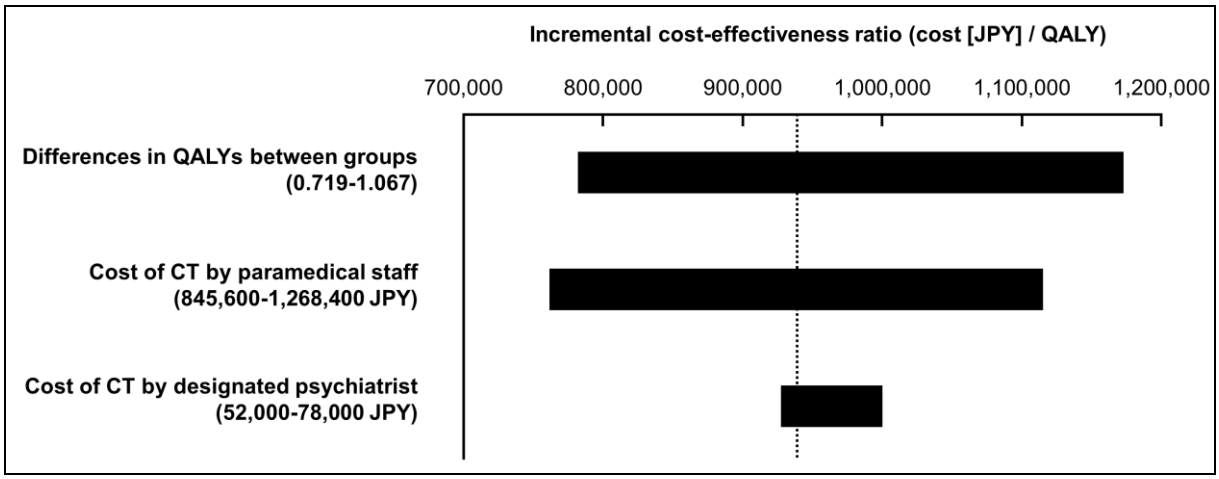


**Figure 1.** Tornado diagram for one-way sensitivity analysis of incremental cost-effectiveness ratio for the primary approach (Approach 1).
*Note: Base case of the ICER for Approach 1 is 938,386 JPY. Each parameter was varied by +/- 20%. Accepted cost-effective threshold of the ICER is 5 million JPY.*

Results suggest that, from the public healthcare payer's perspective, adding CT for refractory SAD was found to be highly cost-effective. The cost-effectiveness was robust when considering results from the sensitivity analysis using different assumptions. Previous model-based economic analyses revealed that individually delivered CT based on the Clark and Wells model was the most cost-effective treatment among various psychological and pharmacological interventions for SAD, with the highest Net Monetary Benefit at the UK lower cost effectiveness threshold, despite having the highest intervention cost [5]. However, as the current study is the first economic analysis of adjunctive CT for antidepressant-refractory SAD, it's difficult to directly compare our findings with previous studies. Our economic analysis was based on one-year follow-up observations, but several

studies which employed individual CT using face-to-face or internet sessions demonstrated that improvements gained were maintained for four to ten years after treatment was completed [6-8]. Considering that individual CT is effective in SAD treatment, regardless of whether the case is antidepressant-refractory [3], economic analyses based on observations longer than one-year may demonstrate even higher total cost-effectiveness by adding CT treatment to usual care specifically for antidepressant-refractory SAD. The main limitation of our economic analysis is that, after week 16, the QALYs in the UC alone group were assumed to be stable. This assumption may be justified, however, since: (a) longitudinal studies indicate considerable chronicity for SAD [9]; (b) long-term, repetitive administration of antidepressants leads to loss of its therapeutic effect [10, 11]; and (c) at present there is no effective next-step treatment option for antidepressant-refractory SAD aside from individual CT.

Although the addition of CT to usual care for antidepressant-refractory SAD involves additional cost, the intervention may still be cost-effective depending on society's willingness to pay for the additional health gain. It has been reported that patients with SAD tend to avoid seeking treatment and incur lower direct costs [12, 13]. From a clinical perspective, it can be argued that an increase in health care utilisation might indicate improvements since patients are seeking adequate treatments. Therefore, elevated costs might be justifiable given the benefits. Although the intervention costs are substantial, these estimates reflect the actual costs of delivering short-term CT in routine outpatient care in Japan according to the FY2016 health insurance scheme (up to 16 individual sessions) and, therefore, represent typical Japanese clinical practice.

The present cost-effective analyses have several limitations. First, as stated, the lack of follow-up data in the UC alone group certainly weakens the reliability of results. Second, the study results are based on a clinical trial that enrolled a relatively small number of patients. Therefore, concerns about the generalisability of the results may be raised. Third, while our economic analyses attempted to capture key features of treatment and costs encountered in managing antidepressant-refractory SAD, some simplifying assumptions had to be made due to the limited availability of information regarding usual care provided by local primary psychiatrists as well as indirect costs. To evaluate outcomes with more confidence, a replication study is needed which employs a larger sample size and evaluates more information such as indirect costs and concurrent medication.

Thus, the results of the economic analyses suggest that adding CT to usual care for antidepressant-refractory SAD seems to be a cost-effective treatment. However, no valid conclusions can be drawn, since there was no assessment of follow-up clinical outcome data in the UC alone group, direct costs of usual care during or after treatment, and/or the indirect costs after treatment.

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