**Optimal Treatment for OCD Trial (OTO Trial)**

**Final Data Report**

**Final Version 1.0 29th June 2018**

**Sponsor Protocol Number: LMS/SF/UH/00018/AM4**

**EudraCT Number: 2013-003219-22**

**REC reference: 13/EE/0431**

Table of Contents

List of Figures3

List of Tables3

**1.0 Trial Objectives/Endpoints5**

1.1 Data Analysis - Methods6

1.1.1 Feasibility of Recruitment6

1.1.2 Process Evaluation7

1.1.3 Safety7

1.1.4 Resource use and quality of life8

1.1.5 Evaluation of Outcome Measures12

**2.0 Results12**

2.1 Summary of feasibility assessment12

2.2 Clinical Outcome Measures12

2.2.1 Primary Outcome25

2.2.2 Secondary Outcome Measures25

2.3 Patient Interview Report33

2.4 Safety34

2.5 Health Economic Data35

**3.0 Discussion50**

Feasibility52

Effectiveness52

**4.0 Conclusions54**

Implications56

**References56**

**Appendices58**

Appendix A: Breakdown by Centre58

Appendix B: Review of Audio Files, Dr Lynne Drummond63

**List of Figures**

Figure 1: Study Flow Chart13

**List of Tables**

Table 1: Patients at screening15

Table 2: Patients randomised15

Table 3: Patient Characteristics16

Table 4: Patient Baseline Data…………………………………………………………………………………………………………………….17

Table 5: Noted Psychiatric Comorbidity and Concomitant Medications17

Table 6: Time Lag between randomisation and start of CBT therapy18

Table 7: Patient progression through study protocol following randomisation19

Table 8: Patient Adherence to treatment protocol20

Table 9: Reasons for non-compliance to treatment protocol21

Table 10: Breaking of allocation blinding22

Table 11: Data completion for outcome measures23

Table 12A: Total Y-BOCS scores on CBT, sertraline and combined treatment; observed case analysis and intent to treat analysis……………………………………………………………………………………………………………………..………....27

Table 12B: Total MADRS scores on CBT, sertraline or combined treatment; observed case analysis and intent to treat analysis28

Table 12C: CGI Severity, CGI improvement and Sheehan Disability Scale scores on CBT…29

Table 12D: Autism Quotient, EQ5D and CANTAB scores on Sertraline, CBT or combined treatment 30

Table 13: Scale Characteristics32

Table 14: Frequency of adverse events reported during the trial34

Table 15: Serious adverse events35

Table 16: Serious adverse reactions35

Table 17: Suspected unexpected serious adverse reactions35

Table 18: Questionnaire completion rates – EQ-5D and resource use37

Table 19: Number of sertraline-related appointments attended and mean sertraline dosage prescribed (available case unless stated otherwise, over the 52 week follow up period)39

Table 20: Number of CBT sessions attended (available case unless stated otherwise, over the 52 week follow up period)40

Table 21: Estimated unit costs, with associated sources41

Table 22: Total intervention costs per participant (available case, total across participants over specified follow up periods)42

Table 23: Level of resource use 44

Table 24: Total costs 45

Table 25: Mean total costs per participant 46

Table 26: Outcomes (available case, per participant) 47

Table 27: Estimates of incremental cost, incremental effect and net monetary benefit and sensitivity analysis for sertraline monotherapy compared to CBT monotherapy and combination therapy 48

**Optimal Treatment for OCD Trial (OTO Trial)**

**Final Data Report**

## TRIAL OBJECTIVES/ENDPOINTS

The aim of the trial was to recruit a target sample of 60 people with obsessive-compulsive disorder (OCD) to participate in a feasibility study to inform the design of a definitive trial determining the clinical and cost effectiveness of combining CBT with SSRI versus either treatment given alone, to improve service delivery for people with OCD.

The objectives of this trial were:

1. Feasibility of recruitment

* To assess the willingness of clinicians/services to randomise patients
* To evaluate the number of patients referred/screened/eligible/willing to be randomised across the three centres, according to referral source.
* To evaluate the differences in methods of identifying/recruiting patients.

1. Process Evaluation

* To evaluate the practicality of delivering the intervention in the proposed setting.
* To evaluate methods to ensure protocol fidelity eg. CBT models, rater blindness
* To evaluate the variation in delivery of the intervention in each setting
* To investigate premature discontinuation rates and their reasons across the three treatment arms and the three participating centres.
* To evaluate the extent of missing data
* To evaluate the facilitators and barriers to participation in the trial.

1. Safety

* To evaluate treatment-related adverse events and tolerability across the treatment arms.

1. Resource use and quality of life

* To monitor resource use and quality of life changes to inform the decision as to how costs and benefits should be measured as part of any future, more definitive, study. A preliminary cost-effectiveness analysis was also undertaken.

1. Evaluation of Outcome Measures

* To evaluate the endpoints to enable appropriate estimation of the sample size required for a full-scale trial.
  1. **Primary Endpoint:** To estimate the variation of the primary outcome measure, the Y-BOCS1, both within and between the three treatment arms
  2. **Secondary Endpoint:** To evaluate the influence of the following outcomes on patient selection and on the primary end point, to inform minimisation strategies in the subsequent definitive trial, and the need for adjusted and stratified analysis.
  + CGI Severity Scale and CGI Improvement scale
  + Sheehan Disability Scale (SDS)2
  + Montgomery Asberg Depression Rating Scale (MADRS)3
  + CANTAB - Stop-signal reaction time, id-ed, affective go-no go; Cambridge gamble task.
  + The Autism Quotient (AQ)

## DATA ANALYSIS - METHODS

All analysis followed the relevant CONSORT4 5 reporting criteria, and has addressed each of the 5 aims in turn.

### FEASIBILITY OF RECUITMENT

***[Figure 1 and Tables 1 to 6]*** The flow of patients through recruitment to randomisation has been recorded, and the numbers of patients falling into each group evaluated. A standard flow chart illustrates the flow of patients through the recruitment process. The potential differences in the sources of recruitment as an indication of willingness to refer and randomise patients have been evaluated. As there is a relatively small number of randomised patients, analysis is restricted, so the primary focus is descriptive (averages (proportions) and confidence intervals).

### PROCESS EVALUATION

***[Tables 7 to 13]*** Analytically the primary focus of this analysis was to determine the extent to which completion rates[[1]](#footnote-2) differ by study arm and by treating centre. The analysis is initially descriptive to highlight potential sources of variation between the study arms and treating centres. Further evaluation, using appropriate paired comparisons, or regression models (logistic, or linear) determined the potential magnitude of any differences that are apparent. The analysis seeks to provide evidence for the limits of the ICC describing differences between the groups to inform the design of the definitive study.

The analysis seeks to characterise the acceptability of the study to the patients by estimating the proportions of patients who agree to participate, or not, those withdrawing from randomised treatment, and agreeing to continue with the trial measures despite withdrawing from randomised treatment. The degree of adherence to the randomised treatment has also been evaluated to inform future trial design.

Reasons for discontinuation were recorded where possible on the study Withdrawal Form in the CRF. The reasons given were summarised and common themes sought. The themes arising have been evaluated to determine whether the study design could be modified, or service delivery modified to improve study retention.

Instances of unblinding and other protocol violations, recorded during the study have been tabulated, and the influence of substantial variation considered in relation to the primary outcome.

A report on the patient interviews conducted has been included.

### SAFETY

***[Tables 14 to 17]*** Reported safety events are defined in section 9 of the trial protocol. Safety events have been tabulated by arm, and examined to provide evidence of difference in the safety profile of the 3 study arms. Where significant variation between study arms is found, and sufficient numbers of events are reported analytical methods have been applied to evaluate any apparent differences (eg the relative frequency of events, life tables, and Poisson models). The standard MHRA (<http://www.ct-toolkit.ac.uk/routemap/safety-reporting/>) reporting procedures have been followed to provide consistency in reporting.

### RESOURCE USE AND QUALITY OF LIFE

***[Tables 18 to 27]*** All costs were estimated for the 2015/2016 financial year and no discounting was undertaken as the follow up period was one year.

Intervention costs

*Sertraline appointments*

Those randomised to receive sertraline were scheduled to attend appointments at weeks 0, 2, 4, 8, 16, 24, 32 and 52; with a view to be prescribed sertraline which was to be flexibly titrated upwards from 50mg to 200mg. Participants were seen by a specialist registrar, who recorded attendance and sertraline dosage prescribed. Appointments were assumed to last 30 minutes, with an additional 30 minutes of indirect non-contact registrar time required per appointment. No additional training, travel or equipment was required. Specialist registrars also met with a local consultant psychiatrist for an average of 5 mins per session for supervision purposes (this would include a discussion of patient adherence / compliance). Unit costs were subsequently assigned to these appointment / supervision times, where the cost per hour of employment was estimated to be £71.84 for a specialist registrar and £106.71 for a consultant psychiatrist (based on an annual salaries of £47,64713 and £89,8048, respectively). This enabled the total per patient cost of sertraline appointments and supervision to be estimated.

*Sertraline medication*

The actual cost to the NHS of sertraline medication was estimated using the NHS Business Services Authority actual cost formula14, based on the March 2016 tariff with a national average discount of 7.43%. This enabled the monthly medication cost for each dose of sertraline to be estimated (including any combinations e.g. a dosage of 50mg and 100mg was required for a dosage of 150mg) where an additional constant fee of £1.01 (pharmacist professional fee of £0.90 and a packaging /container cost of £0.11, regardless of the dosage and/or length of the prescription), was added to this cost to in order to estimate the per prescription cost. When combined with prescription information (dosage and frequency, as recorded by the specialist registrar) this enabled the total cost of prescribed sertraline to be estimated.

It was assumed that registrars prescribed enough sertraline to last participants from the date of each appointment, until their next scheduled appointment, in preference to regular monthly prescriptions. Registrars could also recommend that the dosage of sertraline be further increased before the participant’s next appointment; we were advised that if such an increase was recommended, this occurred at the half way point between appointments. If there was no recorded increase it has been assumed participants remained on the same dosage until their next appointment. It was also assumed that if a participant missed a scheduled appointment, they continued to take their medication (at the most recently prescribed dosage) until their next visit and that the health professional in question would have made every effort to ensure they had sufficient supplies to do this. If a participant ceased to attend any further scheduled appointments it has been assumed they did not continue to take sertraline throughout the remainder of the trial, and there were no further prescription costs. The prescription issued on the final visit has been costed under the assumption that even if it had not been taken, the sertraline could not be re-dispensed once it had left the pharmacy and therefore was funded by the NHS. For example, if a participant had inclusively attended all previous appointments until week 24, they have been costed to receive 32 weeks’ worth of sertraline. Prescriptions issued at week 52 have been costed as one month of sertraline; this can be justified under the assumption that the cost was incurred at the time of the appointment, which falls within the annual time frame of the analysis. Unit costs were subsequently attached to each reported prescription item (see above). The costs associated with the aforementioned appointments, supervision and prescribed sertraline were then summed to estimate the total cost of sertraline.

*CBT Sessions*

Participants randomised to CBT were offered eight weekly 1:1 CBT sessions, with follow up sessions at weeks 16, 24, 32 and 52. The therapists who took these sessions recorded attendance and the contact time of each session. It was additionally assumed that one extra hour of non-contact staff time was required per session, regardless of length, but that no additional equipment or travel would be required. Unit costs were assigned to all attended sessions (costed at the combined average earnings of: speciality doctor, clinical psychologist and mental health nurse8), enabling the total cost of CBT sessions to be estimated.

*CBT Training and supervision*

It was assumed each therapist (two per site) required two hours of joint CBT training (occurring once per site), where the training was provided by a local consultant psychiatrist (see aforementioned costs8). The therapists were also assumed to receive one hour supervision per month, with the same consultant psychiatrist, throughout the 29 month trial therapy provision period. The above enabled the total cost of both training and supervision to be estimated; these were equally apportioned across all those allocated to a CBT option (N=34 participants) to derive a training and supervision cost per participant. As trainers were local consultant psychiatrists, there were no associated travel costs. As patients received therapy on a weekly basis, compliance phone calls to patients between visits were also infrequent and classified as a negligible cost.

The total cost of CBT sessions, training and supervision were summed to estimate the total cost of CBT.

*Overall intervention costs*

The intervention costs for each of the three treatment options were subsequently estimated, where the mean total cost of sertraline was estimated for those assigned to sertraline monotherapy, the mean total cost of CBT was estimated for those assigned to CBT monotherapy, and the mean total cost of sertraline plus CBT was estimated for those assigned to sertraline plus CBT (combined option).

*Other NHS and PSS costs*

At baseline and subsequent in-person follow up visits (at 16 weeks and 52 weeks post randomisation), participants were asked if they had received a selection of health care related services as described below; each questionnaire referred to resources used within the previous 16 weeks only (enabling resource use to always be estimated over a common time period).

A researcher completed the resource use questionnaires based on verbal responses from each participant. For each resource use item a “Yes” or “No” option was available. Where “No” was reported, the total cost for that item was assumed to be zero and if the question was not answered it was assumed to be missing. If a participant answered “Yes”, they were asked to report the level of resource use as described below. In order to maintain blinding participants were asked to exclude any therapy intervention visits from their responses to this questionnaire.

Participants were asked whether they had seen, or had contact, with any health care professional (including social care and any phone calls/outpatient visits) in the 16 weeks prior to each questionnaire completed. Those who responded ‘Yes’, were asked to provide details as to the profession of the person seen/contacted, the total number of visits/phone calls in the specified period and where the majority took place. As discussed above, we have assumed intervention related contacts were not included. Unit costs e.g.8,15 were subsequently assigned to all visits/phone calls. The costs were then summed to estimate the total health professional contact cost at the different follow up periods.

Participants were asked if they had been admitted to hospital or another unit of care within each follow up period. Those that answered yes were asked to provide, for each admission, the admission and discharge date - this enabled the length of stay to be estimated. A unit cost per bed day16 was subsequently assigned to each day of admission, enabling the total hospital admission cost to be estimated.

Participants were asked if they had experienced any other care from the health service or social services, excluding previously reported items e.g. accident and emergency (A&E) visits or day case procedures. Those that answered “Yes” were asked to report the total number of each type throughout the specified follow up period. Unit costs16 were then assigned to each item in order to estimate the total other costs from the health service or social services.

Finally, participants were asked if they had received any help from a carer, friend/family member, or any other person. Those who responded “Yes” were asked who provided the care e.g. professional carer, family member/friend or any other person, the average number of hours per week that care was provided and whether a payment was made for any of these services. When answering this subsection of the questionnaire, participants were asked not to report any help from health professionals that had been previously reported in the questionnaire to prevent double counting. For the purposes of the base-case analysis (which was from an NHS and Personal Social Services (PSS) perspective), costs were only included if care was provided by a professional carer and were not paid for by the participant. This enabled the total NHS / PSS professional carer cost to be estimated.

*Outcomes*

In line with the National Institute for Health and Clinical Excellence (NICE) methods guide,9 quality of life was measured using the EQ-5D-3L6. Participants were asked to complete this at the initial (baseline) consultation and again at the 16 weeks and 52 weeks follow-up. Responses were converted into utility scores (a scale where zero is equal to death and one is full health)17 using the York A1 tariff10. Quality Adjusted Life Year (QALY) scores were subsequently calculated for the 52 week follow-up period using the total area under the curve approach18 where a QALY score could be estimated for all those who completed the EQ-5D-3L at baseline, 16 weeks and 52 week follow up points. No discounting was undertaken as the follow up period was one year.

*Analysis*

To inform the decision as to how costs and benefits might be estimated in any subsequent more definitive study completion rates and large cost drivers were estimated. Preliminary cost-effectiveness analysis was also conducted, where the results should be treated with caution due to the small numbers in each group. The analysis is however justified by the argument that decisions need to be made, regardless of the quality of the data, and the mean estimates constitute the best evidence available19. The base case analysis was undertaken from the perspective of the NHS and PSS perspective as recommended by NICE9.

Intervention data were recorded throughout the 52 week follow up period and the annual intervention cost was estimated using the methods aforementioned. However as the questionnaire only requested other NHS and PSS resource use data for the last 16 weeks at the 16 week and 52 week follow up points i.e. the first and last 16 weeks in the annual period post randomization, resource use data for the 20 weeks in between was not collected. In order to estimate the cost of resource use within these 20 weeks, the average weekly cost of the first and last 16 weeks was calculated, and subsequently multiplied by 20. This 20 week cost was added to the cost of the other NHS and PSS costs for the last 16 weeks at the 16 week and 52 week follow up points, in order to estimate the total annual other NHS and PSS costs. This in turn was added to the total intervention costs to estimate the overall annual cost to the NHS and PSS which has been used in the base case analysis.

In the base-case analysis a complete case approach20 was undertaken, whereby participants were only included if the aforementioned overall annual cost to the NHS and PSS and QALY score could be calculated. As such if any one of the resource use costs could not be estimated, at any time point, then the participant would not be included in the analysis, regardless of whether other costs and the QALY score could be estimated. For those participants with complete data over 52 weeks, the mean overall cost and mean effect were estimated. A bivariate regression21 was then undertaken to estimate the mean difference in overall cost to the NHS and PSS and mean difference in QALYs between each of the three different treatment options. This technique is generally robust for skewed data and allows for any correlation between costs and effects21. Cost and effect regression analyses were run simultaneously, with age, sex, ethnicity, marital status, living situation and education included as covariates, plus the baseline EQ-5D score for the QALY regression.

The above enabled the mean incremental cost and incremental effect between the different treatment options to be estimated, and these were used to estimate which option constituted best value for money. First dominated options were ruled out on the basis that another (dominant) option had both a higher mean effect and a lower mean cost. The incremental cost-effectiveness ratio (ICER) (mean incremental cost/mean incremental effect) was subsequently estimated for the remaining options17, and we considered that an estimated ICER below £20,000 would suggest that the intervention constituted value for money.

In order to estimate the level of uncertainty associated with the decision regarding cost-effectiveness, bootstrap resampling22 (with 5000 replications) was used to estimate the cost effectiveness acceptability curve (CEAC)22. The CEAC depicts the probability of the intervention being cost-effective at various “willingness to pay” thresholds compared to standard care. Here the probability was estimated at a λ (threshold) value of £20,000 per QALY.

*Sensitivity Analysis*

Sensitivity analyses17 were undertaken to assess the robustness of conclusions to changes in key assumptions. In the first sensitivity analysis (SA1), we excluded the intervention costs related to staff training, under the assumption that these costs would not need to be incurred again if the intervention continued in current sites (best case scenario). In the second sensitivity analysis (SA2), overall NHS and PSS costs and QALYS were re-run following multiple imputation23 to account for missing cost and outcome data. We performed multiple imputation in a single model using the “mi impute” command in Stata 14. Imputation took place in twenty cycles, the estimates from which were then pooled and calculated using Rubin’s rules24. Finally, in order to assess how results might change if a wider cost perspective were taken, the final sensitivity analysis (SA3) overall costs included any help from family/friends or any other person that participants reported receiving, where the reported hours of care were assigned the mean hourly pay for all employees25.

### EVALUATION OF OUTCOME MEASURES

***[Tables 12 and 13]*** As a feasibility study the aim of the analysis was to describe the characteristics of the outcome measures. The primary outcome measure have been summarised using means and standard deviations across the study arms to inform estimation of the differences in effect between the study arms. Cocks and Torgersons’ method has been followed to demonstrate that the limits of the estimated effect size are within d'= .3 to .4, and >0, giving confidence that a full scale trial can be designed using these parameter limits.

Secondary outcomes have been evaluated to inform the extent to which they moderate the estimates of difference between the study arms, and whether they should be used in the subsequent definitive trial. Regression models were used to provide evidence of moderation.

Intention to treat (ITT) analysis of the study population was also undertaken to examine the extent to which the observed case findings could be confirmed. Allowing for the small sample size the ITT analysis was evaluated as a mixed model with unstructured variance and appropriate interaction terms29. The outcome of the ITT analysis is presented as adjusted mean group difference for the main study outcomes (YBOCS, MADRS, and CGI), and variation between the observed and adjusted differences are examined to determine the influence of missing data.

1. **RESULTS**

**2.1 SUMMARY OF FEASIBILITY ASSESSMENT**

The data reported in the pages that follow will be used to provide an overall assessment of the likelihood that a definitive trials can successfully be delivered, and any modifications that may be needed to address issues that have been raised during the feasibility study.

**Figure 1: Study Flow Chart**

Assessed for eligibility1 (n= 258 )

Excluded (n=209)

  Not meeting inclusion criteria(n=59)

  Declined to participate (n=150)

  Other reasons (n=0)

Randomized (n= 49)

## Enrollment

## Sertraline

## Allocation

Allocated to intervention (n=18)

 Received (n=15)

 Not received (n=3)

Allocated to intervention (n=15)

 Received (n=14)

 Not received (n=1)

Allocated to intervention (n=16)

 Received (n=15)

 Not received (n=1 )

## Combined

## CBT

Lost to follow-up (n=0)

Discontinued intervention2 (n=3)

Withdrew from study (n=3)

Other (n=1)

## 8 Week Follow-Up

Lost to follow-up (n=1)

Discontinued intervention2 (n=0)

Withdrew from study (n=3)

Other (n=2)

Lost to follow-up (n=0)

Discontinued intervention2 (n=0)

Withdrew from study (n=1)

Other (n=3)

Lost to follow-up (n=0)

Discontinued intervention2 (n=4)

Withdrew from study (n=4)

Other (n=1)

## 16 Week Follow-Up

Lost to follow-up (n=1)

Discontinued intervention2 (n=0)

Withdrew from study (n=4)

Other (n=3)

Lost to follow-up (n=1)

Discontinued intervention2 (n=3)

Withdrew from study (n=3)

Other (n=3)

Lost to follow-up (n=0)

Discontinued intervention2 (n=4)

Withdrew from study (n=9)

Other (n=1)

## 32 Week Follow-Up

Lost to follow-up (n=3)

Discontinued intervention2 (n=0)

Withdrew from study (n= 6)

Other (n=0)

Lost to follow-up (n=3)

Discontinued intervention2 (n=4)

Withdrew from study (n=4)

Other (n=1)

Lost to follow-up (n=0)

Discontinued intervention2 (n=4)

Withdrew from study (n=9)

Other (n=0)

## 52 Week Follow-Up

Lost to follow-up (n=3)

Discontinued intervention2 (n=0)

Withdrew from study (n=6)

Other (n=0)

Lost to follow-up (n=4)

Discontinued intervention2 (n=5)

Withdrew from study (n=4)

Other (n=0)

Analysed wk8 n=14 wk52 n=9  
 Excluded from analysis   
wk8 n=4 wk52 n=9

## Analysis

Analysed wk8 n=9 wk52 n=6  
 Excluded from analysis   
wk8 n=6 wk52 n=9

Analysed wk8 n=12 wk52 n=8  
 Excluded from analysis   
wk8 n=4 wk52 n=8

Notes:

1. Total N is defined as all unique patient IDs on the study data base
2. Patients who deviated from protocol treatment but continued on study
3. Other is defined as patients who did not attend at that time point

**Table 1: Patients at screening**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | N | Centre | | |
| HPFT | SWSG | SHTN |
| Identified as potentially suitable# | 258 | 110 | 110 | 38 |
|  |  |  |  |  |
| Referral Source |  |  |  |  |
| IAPTS | 48 | 48 | 0 | 0 |
| GP/Primary Care | 24 | 13 | 5 | 6 |
| Secondary/Tertiary Care | 93 | 34 | 40 | 19 |
| Self | 92 | 14 | 65 | 13 |
| Other - University | 1 | 1 | 0 | 0 |
|  |  |  |  |  |
| Eligible for Assessment | 199 | 86 | 80 | 33 |
| Agreed to be assessed | 77 | 35 | 18 | 24 |
| Screened | 66 | 29 | 14 | 23 |
| Required washout | 31 | 13 | 9 | 9 |
|  |  |  |  |  |
| Excluded | 59 | 24 | 30 | 5 |
| Reasons for exclusion |  |  |  |  |
| Age <18 or >65 | 2 | 0 | 1 | 1 |
| Other Diagnosis (MINI) | 15 | 7 | 7 | 1 |
| MADRS >30 | 3 | 1 | 1 | 1 |
| Treatment resistant | 3 | 2 | 0 | 1 |
| Co-morbidities | 4 | 4 | 0 | 0 |
| Pregnant/breastfeeding/Trying for a baby | 9 | 6 | 3 | 0 |
| Epilepsy | 1 | 1 | 0 | 0 |
| History of suicidality | 1 | 1 | 0 | 0 |
| On other research study | 1 | 0 | 1 | 0 |
| Receiving CBT | 4 | 0 | 4 | 0 |
| Inadequate English | 1 | 0 | 1 | 0 |
| Requires psychotropic medication | 3 | 0 | 2 | 1 |
| On anti-psychotic medication | 1 | 0 | 1 | 0 |
| On lithium | 2 | 0 | 2 | 0 |
| On medication for ADHD | 1 | 0 | 1 | 0 |
| OCD too mild | 7 | 2 | 5 | 0 |
| No reason given | 1 | 0 | 1 | 0 |
| Declined to participate | 150 | 62 | 72 | 16 |
| Wanted to choose arm | 38 | 25 | 12 | 1 |
| Difficulties attending | 36 | 15 | 14 | 7 |
| Did not want to wash out | 21 | 9 | 9 | 3 |
| Reasons unknown | 23 | 0 | 21 | 2 |
| Did not respond to invite | 15 | 7 | 6 | 2 |
| Not interested in research | 8 | 5 | 3 | 0 |
| Did not complete wash out | 1 | 1 | 0 | 0 |
| Unhappy with treatment options | 1 | 0 | 0 | 1 |
| Happy with current treatment | 5 | 0 | 5 | 0 |
| Other: Not ready | 2 | 0 | 2 | 0 |

Note: *Other listing* – Many classifications (eg Declined to participate) come from open responses. These responses will be grouped into a limited number of themes

#“Patients identified as potentially suitable” were all given a unique id on the database

**Table 2: Patients randomised**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Centre | N | Study arm | | | average per month |
| Sertraline | CBT | Combined |
| HPFT | 24 | 8 | 8 | 8 | 1.1 |
| SWSG | 8 | 2 | 3 | 3 | 0.4 |
| SHTN\* | 17 | 5 | 5 | 7 | 1.1 |

\* SHTN recruited over 15 months rather than 21months

**Table 3: Patient Characteristics**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | HPFT | SWSG | STSN |  | Sertraline | CBT | Combined |
| N | 49 | 24 (49%) | 8 (16%) | 17 (35%) |  | 15 (31%) | 16 (33%) | 18 (36%) |
| Male/Female | 21/28 | 11/13 | 4/4 | 6/11 |  | 8/7 | 6/10 | 7/11 |
| % | 43/57 | 46/54 | 50/50 | 35/65 |  | 53/47 | 38/62 | 39/61 |
| Ethnicity |  |  |  |  |  |  |  |  |
| White | 43 (88%) | 22 (92%) | 7 (88%) | 14 (82%) |  | 12 (80%) | 15 (94%) | 16 (89%) |
| Black | 1 (2%) | - | - | 1 (6%) |  | 1 (6%) | - | - |
| Asian/Oriental | 2 (4%) | - | 1 (12%) | 1 (6%) |  | 1 (6%) | - | 1 (6%) |
| Other | 3 (6%) | 2 (8%) | - | 1 (6%) |  | 1 (7%) | 1 (6%) | 1 (6%) |
| Living Status |  |  |  |  |  |  |  |  |
| Divorced | 3 (6%) | 1 (4%) | - | 2 (12%) |  | 1 (7%) | 2 (13%) | - |
| Partnership | 10 (20%) | 5 (21%) | 2 (25%) | 3 (18%) |  | 4 (27%) | 2 (13%) | 4 (22%) |
| Single | 36 (73%) | 18 (75%) | 6 (75%) | 12 (71%) |  | 10 (66%) | 12 (75%) | 14 (78%) |
| Living Situation |  |  |  |  |  |  |  |  |
| Alone | 8 (16%) | 3 (13%) | 1 (13%) | 4 (24%) |  | 2 (12%) | 2 (11%) | 4 (27%) |
| Residence | 2 (4%) | - | - | 2 (12%) |  | - | 1 (6%) | 1 (7%) |
| Family | 22 (45%) | 11 (46%) | 4 (50%) | 7 (42%) |  | 10 (63%) | 10 (56%) | 2 (13%) |
| Friends | 2 (4%) | - | 1 (13%) | 1 (6%) |  | 1 (6%) | - | 1 (7%) |
| Partner | 15 (31%) | 10 (42%) | 2 (25%) | 3 (18%) |  | 3 (19%) | 5 (28%) | 7 (47%) |
| Education |  |  |  |  |  |  |  |  |
| None | 5 (10%) | 1 (4%) | - | 4 (24%) |  | 2 (11%) | 2 (13%) | 2 (11%) |
| O/A Level | 16 (33%) | 9 (37%) | 2 (25%) | 5 (29%) |  | 7 (38%) | 4 (25%) | 7 (29%) |
| Degree | 23 (47%) | 9 (37%) | 6 (75%) | 8 (46%) |  | 7 (38%) | 10 (62%) | 6 (40%) |
| Postgraduate | 5 (10%) | 5 (21%) | - | - |  | 2 (11%) | - | 2 (11%) |
|  |  |  |  |  |  |  |  |  |

The three groups were reasonably well matched at baseline (Table 3). Overall, there was a slight preponderance of females, and most patients were educated at least to university degree level. The mean total Y-BOCS score (26.9 (SD 5.9)) indicated moderately severe OCD. Comorbid depression was diagnosed in 14 patients, though the mean total MADRS score (16.1 (10.1)) indicated the severity of depression was not high in most cases (Table 5). As expected, the most common psychiatric comorbidity was anxiety disorder (n=28). Also present were hoarding disorder (n=7), body dysmorphic disorder (n=5), obsessive-compulsive personality disorder (n=3), skin picking disorder (n=2), hair pulling disorder (n=2) and eating disorder (n=1). Patients were moderately impaired on the SDS, consistent with the community-based nature of the sample. However, the majority were single or divorced (39/49), consistent with the high celibacy rates seen in OCD.

**Table 4: Patient Baseline Data**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | N | All | Randomised/Study Arm | | | | | |
| n | Sertraline | n | CBT | n | Combined |
| Age | 49 | 33.8 (13.0) | 15 | 33.7 (14.0) | 16 | 34.4 (13.1) | 18 | 33.3 (12.8) |
| Y-BOCS | 49 | 26.9 (5.9) | 15 | 26.9 (5.4) | 16 | 26.6 (7.1) | 18 | 27.0 (5.6) |
| CGI Severity | 48 | 4.4 (.96) | 14 | 4.4 (.85) | 16 | 4.2 (1.0) | 18 | 4.4 (.98) |
| SDS | 44 | 18.0 (7.0) | 13 | 18.5 (8.3) | 14 | 16.3 (6.8) | 17 | 19.1 (6.3) |
| Autism Quotient | 47 | 21.7 (6.0) | 15 | 22.4 (5.5) | 15 | 21.0 (6.1) | 17 | 21.8 (6.5) |
| MADRS | 49 | 16.1 (10.1) | 15 | 16.2 (9.8) | 16 | 12.8 (9.7) | 18 | 18.9 (10.4) |
| EQ5D |  |  |  |  |  |  |  |  |
| Health Score | 46 | 55.8 (25.5) | 14 | 58.7 (22.9) | 15 | 50.1 (27.6) | 17 | 58.5 (26.3) |
|  |  |  |  |  |  |  |  |  |
| CANTAB |  |  |  |  |  |  |  |  |
| Stop-Signal | 44 | 228.1 (107.9) | 14 | 234.2 (107.9) | 13 | 256.9 (169.2) | 17 | 201.1 (78.4) |
| ID-ED | 44 | 41.5 (38.7) | 14 | 43.2 (59.4) | 13 | 46.3 (29.1) | 17 | 36.5 (22.0) |
| Go-no-go | 34 | 495.6 (116.6) | 10 | 464.4 (123.5) | 12 | 532.4 (143.1) | 12 | 484.8 (72.9) |
| Gamble Task | 44 | 0.576 (0.159) | 14 | 0.576 (0.173) | 13 | 0.529 (0.140) | 17 | 0.611 (0.161) |

Appendix A reports breakdown by centre.

**Table 5: Noted Psychiatric Comorbidity and Concomitant Medications**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  | n | Centre | | |
| HPFT (n.24) | SWSG (n.8) | SHTN (n.17) |
| **Comorbidity** |  |  |  |  |  |
| Depression |  | 14 | 8 | 2 | 7 |
| Anxiety Disorder |  | 28 | 14 | 9 | 5 |
| Eating Disorder |  | 1 | 0 | 0 | 1 |
| Trichotillomania |  | 2 | 2 | 0 | 0 |
| Hoarding Disorder |  | 7 | 6 | 1 | 0 |
| Body Dysmorphic Disorder |  | 5 | 4 | 1 | 0 |
| Skin Picking Disorder |  | 2 | 1 | 1 | 0 |
| Obsessive Compulsive Personality Disorder |  | 3 | 0 | 2 | 1 |
| **Concomitant Medication** |  |  | 0 | 0 | 0 |
| Antihistamine | baseline | 2 | 1 | 0 | 1 |
| Antihistamine  Antibiotic/Anti-infective agent | In trial | 2 | 0 | 1 | 1 |
| In trial | 1 | 1 | 0 | 0 |
| Antineoplastic Agent | baseline | 1 | 0 | 1 | 0 |
| Asthma Drugs | baseline | 1 | 1 | 0 | 0 |
| Cardiovascular Drugs | baseline | 1 | 0 | 0 | 1 |
| Cardiovascular Drugs  CNS Drugs | In trial | 2 | 1 | 1 | 0 |
|  |  |  |  |  |
| Antidepressants, Benzodiazepines, Anxiolytics, SSRI | baseline | 3 | 1 | 0 | 2 |
| Antidepressants, Benzodiazepines, Anxiolytics, SSRI  Analgesics, Anti-inflammatory, Anti-pyretic, | In Trial | 8 | 5 | 1 | 2 |
| baseline | 4 | 1 | 0 | 3 |
| Analgesics, Anti-inflammatory, Anti-pyretic,  Gastrointestinal Drugs | In Trial | 3 | 1 | 2 | 0 |
| baseline | 5 | 2 | 1 | 2 |
| Hormones and Synthetic substitutes | baseline | 1 | 1 | 0 | 0 |
| Hormones and Synthetic substitutes  Miscellaneous Drugs (Bisphosphonate) | In Trial | 1 | 1 | 0 | 1 |
| baseline | 1 | 0 | 0 | 0 |
| Thyroid and Anti-thyroid Drugs | baseline | 1 | 0 | 1 | 0 |
| Vaccine | In trial | 1 | 0 | 0 | 1 |
| Vitamins | baseline | 2 | 0 | 0 | 2 |
| Vitamins | In trial | 1 | 1 | 0 | 0 |

**Table 6: Time Lag between randomisation and start of CBT therapy**

Range: 7 - 48 days Median: 14 days

|  |  |
| --- | --- |
| **Time in days** | **No of patients** |
| 0-6 | 9 |
| 7-13 | 6 |
| 14-20 | 5 |
| 21-27 | 5 |
| 28-34 | 2 |
| 35-41 | 2 |
| 42-48 | 1 |
| 49 - | 0 |
| Patients withdrawn before starting | 7 |

25 of 34 patients started CBT within 4 weeks, owing to logistical constraints, so most participants completed CBT between week 8 and 16.

**Table 7: Patient progression through study protocol following randomization**

Notes:

Some patients withdrew from treatment but agreed to continue follow-up – these patients are listed as ***Discontinued treatment***

A patient was excluded from the analysis if:

1. The patient was not contactable at the time of the assessment
2. The patient requested to withdraw from the study; but note that patients may have withdrawn from treatment but agreed to continue assessment

Adherence to the treatment protocol (Table 8) was not considered a reason for exclusion, apart from patients who did not take any drug at all, or who did not attend at least one CBT Session.

Appendix A reports breakdown by centre.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | n | Study arm | | |
| Sertraline | CBT | Combined |
| **Randomised** | 49 | 15 | 16 | 18 |
| Did not receive allocated treatment | 5 | 1 | 1 | 3 |
| *Did not want CBT* |  | 0 | 0 | 0 |
| *Did not want drug* |  | 1 | 0 | 1 |
| *Other* |  | 0 | 1 | 2 |
| Received allocated treatment | 44 | 14 | 15 | 15 |
|  |  |  |  |  |
| **8 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 1 | 0 | 0 |
| Withdrawn from study |  | 3 | 1 | 3 |
| Other |  | 2 | 3 | 1 |
| Excluded from Analysis | 14 | 6 | 4 | 4 |
| Discontinued treatment |  | 0 | 0 | 3 |
| Analysed | 35 | 9 | 12 | 14 |
|  |  |  |  |  |
| **16 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 1 | 1 | 0 |
| Withdrawn from study |  | 4 | 3 | 4 |
| Other |  | 3 | 3 | 1 |
| Excluded from Analysis | 20 | 8 | 7 | 5 |
| Discontinued treatment |  | 0 | 3 | 4 |
| Analysed | 29 | 7 | 9 | 13 |
|  |  |  |  |  |
| **32 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 3 | 3 | 0 |
| Withdrawn from study |  | 6 | 4 | 9 |
| Other |  | 0 | 1 | 1 |
| Excluded from analysis | 27 | 9 | 8 | 10 |
| Discontinued treatment |  | 0 | 4 | 4 |
| Analysed | 22 | 6 | 8 | 8 |
|  |  |  |  |  |
| **52 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 3 | 4 | 0 |
| Withdrawn from study |  | 6 | 4 | 9 |
| Other |  | 0 | 0 | 0 |
| Excluded from analysis | 26 | 9 | 8 | 9 |
| Discontinued treatment |  | 0 | 5 | 4 |
| Analysed | 23 | 6 | 8 | 9 |
|  |  |  |  |  |
| Completed the study | 14 | 6 | 3 | 5 |

**Table 8: Patient Adherence to treatment protocol**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | N | Centre | | |
| HPFT | SWSG | SHTN |
| **Combined therapy** |  |  |  |  |
| Returned meds | 3 | 2 | 0 | 1 |
|  |  |  |  |  |
| Total possible CBT Sessions | 144 | 64 | 24 | 56 |
| CBT sessions attended | 134 | 61 | 24 | 48 |
| Completion of treatment hours |  | 89% | 100% | 87% |
|  |  |  |  |  |
| **Sertraline** |  |  |  |  |
| Returned meds | 1 | 1 | 0 | 0 |
|  |  |  |  |  |
| **CBT** |  |  |  |  |
| Total possible CBT Sessions | 128 | 64 | 24 | 40 |
| CBT sessions attended | 104 | 47 | 22 | 34 |
| Completion of treatment hours |  | 88% | 81% | 74% |
| Patients who started OCD medication whilst on study | 4 | 4 | 0 | 0 |
| sertraline | 3 | 3  2 (at wk8)  1 (at wk16) | 0 | 0 |
| fluoxetine | 1 | 1  (at wk24) | 0 | 0 |

Note: N is the number of patients recorded.

The majority of patients on SSRI (29/33; 88%) took study medication as prescribed, as measured by pill-counts on returned packets. The mean daily dose of sertraline prescribed in the SSRI group at week 52 was 166.67mg and in the combination group was 100.00mg.

Adherence to CBT was also found to be acceptable, according to a predetermined criterion of 75%adherence, in 24/34 (71%) cases. There was no difference seen between the arms (see Table 19). For those patients who did not withdraw prematurely, almost all study assessments were completed. Fidelity to CBT was confirmed by random sampling of audiotaped sessions and assessment by a CBT expert (LD) (See Appendix B).

Two patients randomized to combination therapy and one patient randomized to SSRI monotherapy took no study medication (100% non-adherent) as they did not want to take medication. One patient randomized to combination therapy stopped study medication but continued to take a lower dose of sertraline prescribed by their GP. Four patients in the CBT arm started medication (3 sertraline [2 at week 8, 1 at week 16], 1 fluoxetine at week 24] while still on study treatment.

**Table 9: Reasons for non-compliance to treatment protocol**

Medication non-adherence is defined as evidence (returned meds) that fewer than 80% of the tablets were taken as prescribed, or that patients missed more than 25% of CBT sessions, or either for patients on combined therapy.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total** | **HPFT** | **SWSG** | **SHTN** |
| **Combined therapy** |  |  |  |  |
| Medication non-adherence | 3 | 2 | 0 | 1 |
| Did not want drug | 2 | 2 | 0 | 0 |
| Wanted lower dose from GP | 1 | 0 | 0 | 1 |
| CBT Session DNA (no other comment given) | 6 | 0 | 0 | 6 |
| *Work* | 2 | 1 | 0 | 1 |
| *Education* | 1 | 0 | 0 | 1 |
| *Health* | 1 | 1 | 0 | 0 |
| Reduced CBT session length | 32 | 10 | 5 | 17 |
| *no comment given* | 22 | 9 | 4 | 9 |
| *Session complete per protocol* | 1 | 1 | 0 | 0 |
| *Patient symptoms* | 6 | 0 | 1 | 5 |
| *ERP not done (no reason given)* | 2 | 0 | 0 | 2 |
| *ERP not indicated* | 1 | 0 | 0 | 1 |
|  |  |  |  |  |
| **CBT** |  |  |  |  |
| Non-attendance at CBT Session | 24 | 16 | 2 | 6 |
| *DNA (no other comment given)* | 7 | 2 | 0 | 5 |
| *Withdrawn from study* | 11 | 9 | 2 | 0 |
| *Education* | 1 | 1 | 0 | 0 |
| *Health* | 2 | 1 | 0 | 1 |
| *Other* | 3 | 3 | 0 | 0 |
| Reduced CBT session length | 41 | 20 | 8 | 13 |
| *no comment given* | 33 | 18 | 7 | 8 |
| *Session complete per protocol* | 1 | 1 | 0 | 0 |
| *Patient symptoms* | 4 | 1 | 0 | 3 |
| *ERP not done (no reason given)* | 2 | 0 | 0 | 2 |
| *Client work* | 1 | 0 | 1 | 0 |
| **Sertraline** |  |  |  |  |
| Medication non-adherence | 15 | 8 | 2 | 5 |
| *No comment given* | 10 | 5 | 1 | 4 |
| *Non-compliant* | 1 | 1 | 0 | 0 |
| *Forgetting to take meds* | 1 | 0 | 0 | 1 |
| *Seen early* | 2 | 1 | 1 | 0 |
| *Side effects* | 1 | 1 | 0 | 0 |

**Table 10: Breaking of allocation blinding**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Role Unblinded | n | Time Point | Study Arm | | |
| Sertraline | CBT | Combined |
|  |  |  |  |  |  |
| Statistician | 0 |  |  |  |  |
|  |  |  |  |  |  |
| Researcher Site - HPFT | 5 | 3xwk2, 1xwk16, 1xwk52 | 0 | 2 | 3 |
|  |  |  |  |  |  |
| Researcher Site - SWSG | 2 | 2xwk16 | 0 | 0 | 2 |
|  |  |  |  |  |  |
| Researcher Site - SHTN | 9 | 4xwk2, 1xwk4, 2xwk16, 2xwk52 | 2 | 2 | 5 |

**Table 11: Data completion for outcome measures**

Data completion is defined as either:

* A record in the data base for single items outcomes, or
* sufficient data recorded in the database for each patients sufficient to enable estimation of a scale score

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Measure** | **All (%)** | **Centre** | | |
| **HPFT (%)** | **SWSG (%)** | **SHTN (%)** |
| **PRIOR TO RANDOMISATION** | 258 | 110 | 110 | 38 |
|  |  |  |  |  |
| Referral Source | 258 (100%) | 110 (100%) | 110 (100%) | 38 (100%) |
|  |  |  |  |  |
| Exclusion criteria given | 59 (100%) | 23 (96%) | 29 (97%) | 5 (100%) |
|  |  |  |  |  |
| Declined to participate | 127 (85%) | 62 (100%) | 51 (71%) | 14 (88%) |
|  |  |  |  |  |
|  |  | **Study Arm** | | |
|  |  | **Sertraline (%)** | **CBT (%)** | **Combined (%)** |
| **RANDOMISED** | 49 | 15 | 16 | 18 |
| Age | 49 (100%) | 15 (100%) | 16 (100%) | 18 (100%) |
| Sex | 49 (100%) | 15 (100%) | 16 (100%) | 18 (100%) |
| Comorbidity | 49 (100%) | 15 (100%) | 16 (100%) | 18 (100%) |
| Concomitant Medication | 12 | 5 | 1 | 6 |
|  |  |  |  |  |
| **Baseline** |  |  |  |  |
| Y-BOCS | 49 (100%) | 15 (100%) | 16 (100%) | 18 (100%) |
| CGI Severity | 48 (98%) | 14 (93%) | 16 (100%) | 18 (100%) |
| SDS | 44 (90%) | 13 (87%) | 14 (88%) | 17 (94%) |
| Autism Quotient | 47 (96%) | 15 (100%) | 15 (94%) | 17 (94%) |
| MADRS | 49 (100%) | 15 (100%) | 16 (100%) | 18 (100%) |
| EQ5D Health score | 47 (96%) | 14 (93%) | 15 (94%) | 17 (94%) |
| CANTAB |  |  |  |  |
| Stop-Signal | 44 (90%) | 14 (93%) | 13 (81%) | 17 (94%) |
| ID-ED | 44 (90%) | 14 (93%) | 13 (81%) | 17 (94%) |
| Go-no-go | 34 (69%) | 10 (67%) | 12 (75%) | 12 (67%) |
| Gamble Task | 44 (90%) | 14 (93%) | 13 (81%) | 17 (94%) |
|  |  |  |  |  |
| **Week 8** |  |  |  |  |
| Returned medication | 9 (27%) | 3 (20%) | n/a | 6 (33%) |
|  |  |  |  |  |
| Y-BOCS | 35 (71%) | 9 (60%) | 12 (75%) | 14 (78%) |
| CGI Improvement | 35 (71%) | 9 (60%) | 12 (75%) | 14 (78%) |
| SDS | 33 (71%) | 9 (60%) | 10 (63%) | 14 (78%) |
| MADRS | 35 (71%) | 9 (60%) | 12 (75%) | 14 (78%) |
|  |  |  |  |  |
| **Week 16** |  |  |  |  |
| Returned medication | 11 (33%) | 5 (33%) | n/a | 6 (33%) |
| Attended CBT Sessions | 13 (38%) | n/a | 6 (38%) | 7 (39%) |
| Length of CBT Sessions | 15 (44%) | n/a | 7 (44%) | 8 (44%) |
| Completion of homework | 13 (38%) | n/a | 6 (38%) | 7 (39%) |
|  |  |  |  |  |
| Y-BOCS | 29 (59%) | 7 (47%) | 9 (56%) | 13 (72%) |
| CGI Improvement | 29 (59%) | 7 (47%) | 9 (56%) | 13 (72%) |
| SDS | 29 (59%) | 7 (47%) | 9 (56%) | 13 (72%) |
| MADRS | 29 (59%) | 7 (47%) | 9 (56%) | 13 (72%) |
| EQ5D Health score | 29 (59%) | 7 (47%) | 9 (56%) | 13 (72%) |
| CANTAB |  |  |  |  |
| Stop-Signal | 25 (51%) | 6 (40%) | 8 (50%) | 11 (61%) |
| ID-ED | 25 (51%) | 6 (40%) | 8 (50%) | 11 (61%) |
| Go-no-go | 22 (45%) | 5 (33%) | 6 (38%) | 11 (61%) |
| Gamble Task | 25 (51%) | 6 (40%) | 8 (50%) | 11 (61%) |
|  |  |  |  |  |
| **Week 32** |  |  |  |  |
| Returned medication | 5 (15%) | 2 (13%) | n/a | 3 (17%) |
| Attended CBT Sessions | 10 (29%) | n/a | 4 (25%) | 6 (33%) |
| Length of CBT Sessions | 10 (29%) | n/a | 3 (19%) | 7 (39%) |
| Completion of homework | 9 (26%) | n/a | 4 (25%) | 5 (28%) |
|  |  |  |  |  |
| Y-BOCS | 22 (45%) | 6 (40%) | 8 (50%) | 8 (44%) |
| CGI Improvement | 23 (47%) | 6 (40%) | 9 (56%) | 8 (44%) |
| SDS | 22 (45%) | 6 (40%) | 8 (50%) | 8 (44%) |
| MADRS | 23 (47%) | 6 (40%) | 9 (56%) | 8 (44%) |
|  |  |  |  |  |
| **Week 52** |  |  |  |  |
| Returned medication | 5 (15%) | 2 (13%) | n/a | 3 (17%) |
| Attended CBT Sessions | 9 (26%) | n/a | 4 (25%) | 5 (28%) |
| Length of CBT Sessions | 9 (26%) | n/a | 4 (25%) | 5 (28%) |
| Completion of homework | 5 (15%) | n/a | 2 (13%) | 3 (17%) |
|  |  |  |  |  |
| Y-BOCS | 23 (47%) | 6 (40%) | 8 (50%) | 9 (50%) |
| CGI Improvement | 22 (45%) | 6 (40%) | 7 (44%) | 9 (50%) |
| SDS | 23 (47%) | 6 (40%) | 8 (50%) | 9 (50%) |
| MADRS | 23 (47%) | 6 (40%) | 8 (50%) | 9 (50%) |
| EQ5D Health score | 23 (47%) | 6 (40%) | 8 (50%) | 9 (50%) |
| CANTAB |  |  |  |  |
| Stop-Signal | 17 (35%) | 5 (33%) | 6 (38%) | 6 (33%) |
| ID-ED | 17 (35%) | 5 (33%) | 6 (38%) | 6 (33%) |
| Go-no-go | 15 (31%) | 4 (27%) | 6 (38%) | 5 (28%) |
| Gamble Task | 17 (35%) | 5 (33%) | 6 (38%) | 6 (33%) |

**2.2 Clinical Outcome Measures**

**2.2.1 Primary Outcome (Y-BOCS) (Table 12A)**

All treatment arms were associated with a numerical improvement in total Y-BOCS scores over the course of the 52-week study (Table 12A). At Week 16 (primary endpoint) there was a substantial advantage for the combination treatment over CBT (Cohen’s d = .39, CI (-.47, 1.24)) and a more modest advantage for SSRI over CBT (*d* = .27, CI (-.73, 1.3)). At Week 32 and at Week 52, however, there was a marked advantage for SSRI monotherapy when compared both to CBT (*d* (week 32) =. 57, CI (-.52 , 1.7); *d* (week 52) = .56, CI (-.53 , 1.6) and to combination treatment (*d* (week32) = -.49,

CI (-1.6, .59); *d* (week 52) = -.44 CI (-1.5 , .61)).

**2.2.2 Secondary Outcome Measures**

**MADRS (Table 12B)**

Although starting from a numerically lower baseline, the MADRS scores for those in the CBT arm did not improve and were numerically higher than baseline at both Week 16 and Week 52. In contrast, MADRS scores in the sertraline arm improved substantially over the first 8 weeks of treatment and remained low (<10) between week 8 and the 52 week endpoint. In the combination arm, the magnitude of the improvement in the MADRS was less than that for sertraline monotherapy and scores worsened after 16 weeks (Table 12B).

At 16 weeks, the effect size of the difference between the sertraline (mean MADRS= 8.1 (SD 6.5)) and CBT arm (mean MADRS = 14.9 (SD 10.6) was .75 CI (-.29-1.8). At Week 52 the effect size of the difference was .46 CI (-.62 - 1.5). Similarly, at Week 16 the effect size of the difference between the sertraline and the combination arm (mean MADRS=12.6 (SD 9.3)) was .53 CI (-1.5 - .41) and at week 52 it was .59 CI (-1.6 - .48).

**CGI severity, CGI improvement, SDS (See Table 12C)**

*CGI Severity*

Over the 16-week treatment phase, CGIs scores improved similarly in the SSRI and combination arms, but not in the CBT arm. After Week 16, however, the SSRI and the CBT arm showed further improvement but the combination group did not. At Week 52, the mean CGIs scores on sertraline, CBT and combined treatment were respectively 2.2 (SD 1.2), 2.9 (SD 1.8) and 3.2 (SD 1.7).

*CGI Improvement*

Compared to baseline, at Week 16 all three arms were on average ‘minimally improved’ on the CGI-Improvement with a numerical advantage for the combination arm. By Week 52, further improvement was seen to the extent that the SSRI and combination groups were ‘much improved’ to a similar degree, whereas the CBT group was ‘minimally improved’.

*SDS*

The SDS is a self-rated measure of impairment, scored in three domains; family, social and working life, which were totaled to provide a composite score. In the case of missing data in one of the three domains, a pro rata score for that domain was calculated. As some patients did not work, the work domain was not scored, and in these cases a pro rata score was estimated where one of the remaining domains was completed.

Patients in all three groups showed a reduction in symptom-related disability over the course of the study. The maximum rate of improvement occurred in the first 16 weeks. At Week 16, improvement was greatest in the combination arm, next greatest in the SSRI arm and least in the CBT arm, which remained the weakest intervention until the final 52 week endpoint. After 16 weeks, however, the advantage for combined treatment was lost, and at Week 52 the greatest improvement was seen in the SSRI arm.

**Table 12: Evaluation of outcome measures**

# A -Total Y-BOCS scores on CBT, sertraline and combined treatment; observed case analysis and intent to treat analysis

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Study Arm | | |  | Difference between Arms | | |  | Adjusted difference (ITT) | | |
|  | All | CBT | Sertraline | Combined |  | CBT vs Sertraline | CBT vs Combined | Sertraline vs Combined |  | CBT vs Sertraline | CBT vs Combined | Sertraline vs Combined |
| Baseline | 49 | 16 | 15 | 18 |  |  |  |  |  |  |  |  |
|  | 26.7 (5.9) | 26.6 (7.1) | 26.5 (5.2) | 27.0 (5.6) |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| Week 8 | 35 | 12 | 9 | 14 |  | -0.56 (-7.9 , 6.8) | .24 (-5.7 , 6.3) | .79 (-7.7 , 6.1) |  | .8 (-5.1 , 6.7) | 2.0 (-1.8 , 5.7) | 1.2 (-5.0 , 7.4) |
|  | 20.7 (7.5) | 20.7 (7.5) | 21.2 (8.6) | 20.4 (7.3) | d’ | -0.07 (-.80 , .90) | .03 (-.74 , .80) | .10 (-.74 , .94) |  | .1 (-.6 , 1.1) | .25 (-.5 , 1.0) | .15 (-.7 , 1.0) |
|  |  |  |  |  |  |  |  |  |  |  |  |  |
| Week 16 | 29 | 9 | 7 | 13 |  | 2.5 (-7.6 , 12.7) | 3.1 (-4.0 , 10.3) | .6 (-10.3 , 9.1) |  | 3.8 (-.45 , 12.2) | 4.3 (0.0 ,8.6) | .05 (-8.3 , 9.3) |
|  | 18.4 (8.9) | 20.6 (6.8) | 18.1 (12.0) | 17.5 (8.7) | d’ | .27 (-.73 , 1.3) | .39 (-.47 , 1.24) | .06 (-.86 , .98) |  | .42 (-.6 , 1.4) | .55 (-.3 , 1.4) | .05 (-.9 , 1.0) |
| Week 32 | 22 | 8 | 6 | 8 |  | 5.1 (-5.3 - 15.5) | -.13 (-8.6 - 8.4) | -5.3 (-7.2 - 17.7) |  | 4.9 (-3.4 , 13.3) | .3 (-6.2 , 6.7) | -4.6 (-13.0 , 3.7) |
|  | 17.0 (9.1) | 18.6 (5.8) | 13.5 (11.9) | 18.8 (9.6) | d’ | .57 (-.52 , 1.7) | -.02 (-1.0 , .96) | -.49 (-1.6 , .59) |  | .55 (-.5 , 1.7) | .04 (-.9 , 1.1) | -.43 (-1.5 , .7) |
| Week 52 | 23 | 8 | 6 | 9 |  | 6.0 (-6.7 - 18.7) | 1.5 (-9.4 - 12.5) | -4.5 (-7.1 - 16.1) |  | 5.1 (-5.1 , 15.2) | 1.2 (-7.5 , 10.0) | -3.8 (-12.7 , 5.0) |
|  | 15.3 (10.3) | 17.5 (11.1) | 11.5 (10.3) | 16.0 (10.1) | d’ | .56 (-.53 , 1.6) | .14 (-.81 , 1.1) | -.44 (-1.5 , .61) |  | .47 (-.6 , 1.5) | .12 (-.8 , 1.1) | -.37 (-1.4 , .7) |

On the left hand side of the table, the numbers of randomised patients completing each rating point of the study are listed in the row above, and mean total Y-BOCS (SD) listed below.

The middle columns of the table, the mean between-arm differences (CI) are listed together with the effect size (CI) (below) calculated as Cohen’s *d*. An effect size >.3 is marked in bold**.**

The right hand side of the table presents the ITT analysis, reporting adjusted mean group differences, and associated effect size.

# Table 12B -Total MADRS scores on CBT, sertraline or combined treatment; observed case analysis and intent to treat analysis.

**MADRS scores across the trial, and comparison between groups**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Study Arm | | |  | | Difference between Arms | | |  | Adjusted difference (ITT) | | |
|  | All | CBT | Sertraline | Combined | |  | CBT vs Sertraline | CBT vs Combined | Sertraline vs Combined |  | CBT vs Sertraline | CBT vs Combined | Sertraline vs Combined |
| Baseline | 49 | 16 | 15 | 18 |  | |  |  |  |  |  |  |  |
|  | 16.1 (10.1) | 12.8 (9.7) | 16.2 (9.8) | 18.9 (10.4) |  | |  |  |  |  |  |  |  |
|  |  |  |  |  |  | |  |  |  |  |  |  |  |
| Week 8 | 35 | 12 | 9 | 14 |  | | 5.3 (-2.8 - 13.3) | 0.02 (-6.7 - 6.7) | -5.3 (-10.7 - 0.2) |  | 7.0 (-.4 , 14.4) | 7.1 (.05 , 13.8) | .2 (-5.6 , 6.0) |
|  | 11.8 (7.9) | 13.2 (10.2) | 7.9 (6.2) | 13.1 (6.2) |  | |  |  |  |  |  |  |  |
|  |  |  |  |  |  | |  |  |  |  |  |  |  |
| Week 16 | 29 | 9 | 7 | 13 |  | | 6.7 (-3.0 - 16.5) | 2.3 (-6.6 - 11.2) | -4.5 (-12.8 - 3.9) |  | 8.4 (1.7 , 15.1) | 6.6 (1.9 , 11.4) | -1.7 (-8.3 , 4.9) |
|  | 12.2 (9.2) | 14.9 (10.6) | 8.1 (6.5) | 12.6 (9.3) | d’ | | .75 (-.29 , 1.8) | .23 (-.62 , 1.1) | -.53 (-1.5 , .41) |  | .94 (-.1 , 2.0) | .66 (-.2 , 1.5) | -.21 (-1.2, .7) |
|  |  |  |  |  |  | |  |  |  |  |  |  |  |
| Week 32 | 23 | 9 | 6 | 8 |  | | 9.5 (-3.1 - 22.1) | 1.7 (-10.6 - 14.0) | -7.8 (-21.3 - 5.7) |  | 10.6 (3.5 , 17.7) | 6.6 (-1.0 , 14.3) | -4.0 (-11.1 , 3.2) |
|  | 13.3 (11.7) | 16.3 (11.5) | 6.8 (10.2) | 14.6 (12.3) |  | |  |  |  |  |  |  |  |
|  |  |  |  |  |  | |  |  |  |  |  |  |  |
| Week 52 | 23 | 8 | 6 | 9 |  | | 5.2 (-8.0 - 18.4) | -1.8 (-13.9 - 10.3) | -7 (-20.6 - 6.6) |  | 6.0 (-2.4 , 14.4) | 2.4 (-4.1 , 8.8) | -3.6 (-11.8 , 4.5) |
|  | 13.2 (11.5) | 13.9 (11.0) | 8.7 (11.5) | 15.7 (12.2) | d’ | | .46 (-.6 , 1.5) | -.15 (-1.1 , .8) | -.59 (-1.6 , .48) |  | .53 (-.5 , 1.6) | .20 (-.8 , 1.1) | -.31 (-1.3 , .8) |

On the left hand side of the table, the numbers of randomised patients completing each rating point of the study are listed in the row above, and the mean total MADRS (SD) listed below.  
The middle columns of the table, the mean between-arm differences (CI) are listed together with the effect size (below) calculated as Cohen’s d. An effect size >.3 is marked in bold.  
The columns on the right of the table present the ITT analysis, providing adjusted group mean differences, and associated effect sizes.

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Table 12C- CGI Severity, CGI improvement and Sheehan Disability Scale scores on CBT, sertraline or combined treatment;  Observed case analysis and intent to treat analysis** | | | | | | | | | | | | |
|  |  | Study Arm | | |  | Difference between Arms | | |  | Adjusted Difference (ITT) | | |
|  | All | CBT | Sertraline | Combined |  | CBT vs Sertraline | CBT vs Combined | Sertraline vs Combined |  | CBT vs Sertraline | CBT vs Combined | Sertraline vs Combined |
| **Baseline** | 48 | 16 | 14 | 18 |  |  |  |  |  |  |  |  |
| CGI Severity | 4.4 (.96) | 4.2 (1.0) | 4.4 (.85) | 4.4 (.98) |  |  |  |  |  |  |  |  |
| CGI Improvement |  |  |  |  |  |  |  |  |  |  |  |  |
| SDS | 18.0 (7.0) | 16.3 (6.8) | 18.5 (8.3) | 19.1 (6.3) |  |  |  |  |  |  |  |  |
| **Week 8** | 35 | 12 | 9 | 14 |  |  |  |  |  |  |  |  |
| CGI Severity | 4.1 (1.2) | 4.3 (1.2 | 3.7 (1.2) | 4.1 (1.2) |  | .67 (-.47 , 1.8) | .26 (-.72 , 1.2) | .4 (-.67 , 1.5) |  | .6 (-.3 , 1.6) | .6 (-.4 , 1.5) | -.1 (-.8 , .6) |
| CGI Improvement | 3.4 (1.1) | 3.6 (1.4) | 3.2 (0.8) | 3.4 (1.1) |  | 0.4 (-0.7 , 1.5) | 0.2 (-0.8 , 1.2) | -0.1 (-1.0 , 0.7) |  |  |  |  |
| SDS | 12.8 (8.0) | 13.5 (7.7) | 11.8 (7.4) | 13.1 (9.0) |  | 1.7 (-5.7 , 9.0) | .34 (-6.9 , 7.6) | 1.3 (-6..1 , 8.8) |  | 2.4 (-3.7 , 8.5) | 3.7 (-1.9 , 9.3) | 1.3 (-4.7 , 7.3) |
| **Week 16** | 29 | 9 | 7 | 13 |  |  |  |  |  |  |  |  |
| CGI Severity | 3.7 (1.6) | 4.3 (1.0) | 3.4 (2.2) | 3.3 (1.4) |  | .90 (-.86 , 2.7) | 1.0 (-.13 , 2.2) | -.12 (-1.8 , 1.6) |  | .63 (-7 , 2.0) | 1.1 (.2 , 1.9) | .45 (-.9 , 1.8) |
| CGI Improvement | 3.0 (1.3) | 3.6 (1.2) | 3.1 (1.6) | 2.5 (1.1) |  | 0.4 (-1.1 - 1.9) | 1.1 (0.1 - 2.1) | 0.7 (-05 - 1.9) |  | .01 (-1.2 , 1.2) | .77 (-.5 , 2.0) | .76 (-.4 , 1.9) |
| SDS | 11.7 (9.0) | 13.8 (8.3) | 13.5 (9.9) | 9.3 (8.9) |  | .33 (-9.4 , 10.1) | 4.6 (-3.3 , 12.4) | 4.2 (-4.9 , 13.4) |  | .81 (-5.2 , 6.8) | 6.4 (1.2 , 11.6) | 5.6 (-1.0 , 12.1) |
| **Week 32** | 23 | 9 | 6 | 8 |  |  |  |  |  |  |  |  |
| CGI Severity | 3.4 (1.5) | 3.8 (1.1) | 2.8 (1.7) | 3.5 (1.9) |  | .94 (-.62 , 2.5) | .28 (-1.3 , 1.8) | .67 (-1.5 , 2.8) |  | .4 (-.8 , 1.7) | .3 (-1.1 , 1.7) | -.2 (-1.7 , .5) |
| CGI Improvement | 2.7 (1.5) | 2.9 (0.8) | 1.8 (1.2) | 3.25 (2.0) |  | 1.1 (-0.03 - 2.13) | -0.4 (-1.9 - 1.2) | -1.4 (-3.4 - 0.6) |  | .5 (-.8 , 1.7) | -.8 (-2.3 , .7) | -1.3 (-3.0 , .4) |
| SDS | 8.7 (8.8) | 7.9 (5.8) | 7.9 (11.3) | 10.1 (10.2) |  | -.04 (-10.1 , 10.0) | -2.3 (-11.2 , 6.7) | -2.2 (-14.8 , 10.4) |  | .4 (-7.7 , 8.5) | -.6 (-5.8 , 4.6) | 1.0 (-9.4 , 7.4) |
| **Week 52** | 23 | 8 | 6 | 9 |  |  |  |  |  |  |  |  |
| CGI Severity | 2.8 (1.6) | 2.9 (1.8) | 2.2 (1.2) | 3.2 (1.7) |  | .71 (-1.1 , 2.6) | -.34 (-2.2 , 3.9) | 1.1 (-.69 , 2.8) |  | .11 (-1.3 , 1.5) | -.47 (-2.1 , 1.1) | -.57 (-1.7 , .5) |
| CGI Improvement | 2.3 (1.5) | 2.6 (2.1) | 2.2 (1.5) | 2.1 (1.4) |  | 0.4 (-1.6 - 2.4) | 0.5 (-1.4 - 2.3) | 0.06 (-1.3 - 1.5) |  | -.08 (-1.5 , 1.4) | .12 (-1.5 , 1.7) | .20 (-1.1 , 1.5) |
| SDS | 9.3 (10.1) | 9.8 (11.2) | 8.1 (10.7) | 9.7 (9.7) |  | 1.7 (-11.2 , 14.7) | .1 (-10.7 , 10.9) | -1.6 (13.2 , 9.9) |  | 1.2 (-7.6 , 10.1) | 1.0 (-6.0 , 8.0) | .23 (-8.5 , 8.0) |

On the left hand side of the table, the numbers of randomised patients completing each rating point of the study are listed in the row below the mean total rating scale score (SD).

**Table 12D- Autism Quotient, EQ5D and CANTAB scores on Sertraline, CBT or combined treatment**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Study Arm (Mean, sd) | | | | Comparison (n, mean difference, ci) | | |
| Total N | Sertraline | CBT | Comb | Comb vs Sert | Comb vs CBT | Sert vs CBT |
| **Baseline** |  |  |  |  |  |  |  |
| Autism Quotient | 47  21.7 (6.0) | 15  22.4 (5.5) | 15  21.0 (6.1) | 17  21.8 (6.5) |  |  |  |
| EQ5D Health Score | 46  55.8 (25.5) | 14  58.7 (22.9) | 15  50.1 (27.6) | 17  58.5 (26.3) |  |  |  |
| CANTAB |  |  |  |  |  |  |  |
| Stop-Signal | 44  228.1 (107.9) | 14  234.2 (107.9) | 13  256.9 (169.2) | 17  201.1 (78.4) |  |  |  |
| ID-ED | 44  41.5 (38.7) | 14  43.2 (59.4) | 13  46.3 (29.1) | 17  36.5 (22.0) |  |  |  |
| Affective Go-No-Go | 34  495.6 (116.6) | 10  464.4 (123.5) | 12  532.4 (143.1) | 12  484.8 (72.9) |  |  |  |
| Gamble Task | 44  0.576 (0.159) | 14  0.576 (0.173) | 13  0.529 (0.140) | 17  0.611 (0.161) |  |  |  |
| **Week 16** |  |  |  |  |  |  |  |
| EQ5D Health Score | 29  69.9 (20.7) | 7  69.4 (16.9) | 9  65.6 (22.6) | 13  73.2 (22.1) | 3.8  (-16.4, 24.0) | -7.7  (-27.8, 12.5) | -3.87  (-25.9, 18.1) |
| CANTAB |  |  |  |  |  |  |  |
| Stop-Signal | 25  192.1 (55.2) | 6  164.7 (24.4) | 8  205.9 (66.5) | 11  197.1 (57.5) | 32.4  (-20.6, 85.4) | 8.8  (-51.3, 68.9) | 41.2  (-21.4, 103.7) |
| ID-ED | 25  32.2 (23.6) | 6  14.8 (6.6) | 8  45.6 (28.4) | 11  32 (20.7) | 17.2  (-1.5, 35.9) | 13.6  (-10.0, 37.3) | 30.8  (4.8, 56.8) |
| Affective Go-No-Go | 22  518.6 (95.6) | 5  468.4 (144.5) | 6  531.0 (111.7) | 11  534.6 (54.7) | 66.1  (-38.0, 170.3) | -3.6  (-88.4, 81.2) | 62.5  (-111.9, 236.9) |
| Gamble Task | 25  0.541 (0.123) | 6  0.447 (0.130) | 8  0.549 (0.091) | 11  0.587 (0.121) | 0.140  (0.006, 0.274) | -0.038  (-0.145, 0.070) | 0.102  (-0.026, 0.23) |
|  |  |  |  |  |  |  |  |
| **Week 52** |  |  |  |  |  |  |  |
| EQ5D Health Score | 23  68.9 (28.2) | 6  72.3 (34.6) | 8  69.8 (25.3) | 9  65.9 (29.3) | -6.4  (-42.2, 29.4) | 3.9  (-24.6, 32.3) | -2.6  (-37.3, 32.1) |
| CANTAB |  |  |  |  |  |  |  |
| Stop-Signal | 17  189.7 (63.8) | 5  154.5 (28.5) | 6  189.2 (47.7) | 6  219.4 (88.2) | 64.9  (-28.9,158.7) | -30.2  (-121.5,61.0) | 34.7  (-20.6, 89.9) |
| ID-ED | 17  34.9 (30.0) | 5  11.4 (4.0) | 6  54.2 (34.9) | 6  35.3 (25.5) | 23.9  (-2.4, 50.3) | 18.8  (-20.5, 58.2) | 42.8  (6.9, 78.6) |
| Affective Go-No-Go | 15  492.4 (107.6) | 4  480.4 (165.8) | 6  492.6 (119.5) | 5  501.7 (43.0) | 21.3  (-158.4, 201.0) | -9.1  (-137.3, 119.0) | 12.2  (-194.2, 218.6) |
| Gamble Task | 17  0.556 (0.120) | 5  0.496 (0.081) | 6  0.503 (0.127) | 6  0.659 (0.071) | 0.162  (0.059, 0.266) | -0.156  (-0.288, -0.023) | 0.007  (-0.143, 0.156) |

**Table 13: Scale Characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Description | Range/interval | Handling missing item scores |
| Y-BOCS | Higher scores indicate greater severity of OCD symptoms. | (0, 40) |  |
| CGI Severity | Measuure of symptom severity, treatment response and efficacy of treatment. | (1, 7)  (normal-most severely ill patients) | n/a |
| SDS | Assesses functional impairment in work/school, social life and family life. | (0, 30) | <10% missing - pro rata scale score. >10% missing - missing scale score |
| Autism Quotient | Assesses degress to which an adult with normal intelligence has traits associated with the autistic spectrum. Above 32 “clinically significant”. | (0, 50) | <10% missing - pro rata scale score. >10% missing - missing scale score |
| MADRS | Assesses depression; higher scores indicate more severe depression. | (0, 60) | <10% missing - pro rata scale score. >10% missing - missing scale score |
| EQ5D |  |  |  |
| Health Score | 0=worst health you can imagine  100=best health you can imagine | (0, 100) | n/a |
| CANTAB |  |  |  |
| Stop-Signal | A test to measuring response inhibition (impulse control). A lower score is better. | n/a  (estimate of time between go stimulus and stop stimulus to successfully inhibit response) | Refer to scoring method |
| ID-ED | A test of rule acquisition and reversal. A lower score is better. | (0, 441) | Refer to scoring method |
| Affective Go-No-Go | A test assessing information processing biases for positive and negative stimuli. A lower score is better. | n/a  (mean time to respond correctly) | Refer to scoring method |
| Gamble Task | A test assessing decision-making and risk-taking behavior. A lower score indicates more self-control. | (0.5, 0.95) | Refer to scoring method |

**2.3 Patient Interview Report**

*Participants*

Seventeen people (two male) took part in an interview to understand about barriers and facilitators to participation in OTO. This group comprised six patients who did not take part in the study (two ineligible) and 11 who did take part; five received CBT and ERP, two received SSRI and four received both therapies.

*Knowledge about OTO trial*

The patients found out about the study in a variety of ways, including from a healthcare professional already working with them, a support group or a newsletter. All patients understood that the OTO trial was about OCD, but some patients, particularly those who did not take part, had only a basic understanding that it was to try and help people with OCD. The majority of people who took part in the study understood that the OTO trial was comparing different treatments for OCD, and many mentioned medication and/or CBT as the treatments given to different groups of participants.

*Prior experiences of medication, CBT and ERP*

The majority of participants did not have issue with taking medication, if they felt it would help improve their health. Some were wary of side-effects, but stated that wouldn’t stop participation in the OTO trial.

Three (50%) of those who did take not part avoided medications if possible and/or were concerned about the washout period.

Over a third of patients had had CBT before. Most of patients were positive about CBT and half of those who took part expressed a preference for getting CBT in OTO compared to medication.

*Factors affecting participation decision*

Of those who were not randomised:

* two patients who were not randomised were not eligible
* one patient did not state why they did not take part
* one patient wanted to focus on their anxiety and depression which they perceived as a bigger issue than OCD
* one person wanted to have CBT but not medication, and the study felt like a big commitment
* one patient felt that the study would take up too much time and would involve a lot of travel

All those who were randomised wanted to receive help and/or improve understanding about OCD. Three expressed that they had wanted to receive CBT and ERP. Eight participants also expressed a desire to help others through their participation in OTO.

Only two people had previously taken part in a clinical trial and both were not randomised into the study.

For some participants, the effects of OCD on their everyday life was considered when making the decision to participate or not, mostly in relation to having to do rituals when leaving the house or social anxiety. For others, the severity of OCD and the impact on their life helped them to make the decision to participate as they wanted help with their condition. Only one person who did not take part stated that OCD made them not want to take part, i.e. due to anxiety of new places.

When commenting on aspects of the study and their decision to participate or not, most participants replied retrospectively, commenting on their experience, rather than how they perceived these aspects when making their decision. Most participants did not have an issue with the time taken to start therapy, although one participant felt that there was a lot to do and a long time to wait. A minority of participants noted that there were a lot of study visits, or that they found the assessments long or frustrating. The majority of participants commented that the study team was supportive and helpful.

When asked about what might encourage or enable participation, suggestions included:

* hearing from someone who has taken part in a clinical trial e.g. via a video on a website
* greater public visibility
* clearer information about what is involved
* highlighting that people will receive help
* explaining the term ‘clinical trial’ so it doesn’t sound scary

**2.4 SAFETY**

Adverse events are defined in Section 9 of the study protocol, including information about classification, methods for data collection, and reporting

**Table 14: Frequency of adverse events reported during the trial**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **n** | **Study Arm** | | | **Significance** |
| **Combined** | **Sertraline** | **CBT** |
| All reported events | 239 | 124 | 64 | 51 | p=<.001 |
|  |  |  |  |  |  |
| Adverse events | 108 | 42 | 21 | 45 | p=.009 |
| Serious adverse events | 2 | 0 | 1 | 1 |  |
| All adverse events | 110 | 42 | 22 | 46 | p=.61 |
| Attributability not recorded | 18 | 10 | 4 | 4 | p=.14 |
| Adverse reactions | 113 | 72 | 39 | 2 | p=<.001 |
| Serious adverse reactions | 1 | 0 | 1 | 0 | p=.37 |
| Suspected unexpected serious adverse reactions | 0 |  |  |  |  |
| All adverse reactions | 114 | 72 | 40 | 2 | p=<.001 |

Notes: Significance evaluated using χ2.

**Table 15: Serious adverse events**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Timepoint** | **Event** | **Arm** | **Severity** | **Study Drug Action** | **Outcome** | **Relationship To Study Drug** |
| Week 10 | Admission to hospital for termination of pregnancy | SSRI mono | Mild | None | Resolved/Remained on study | Not related |
| Week 21 | Admission to hospital for termination of pregnancy | CBT mono | Mild | None | Resolved/Remained on study | Not related |

**Table 16: Serious adverse reactions**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Timepoint** | **Event** | **Arm** | **Severity** | **Study Drug Action** | **Outcome** | **Relationship To Study Drug** | **Expected** |
|  |  |  |  |  |  |  |  |
| Week 2 | Suicide attempt | SSRI Mono | Life-threatening | Stopped | Resolved/Withdrawn | Possibly related | Yes |

**Table 17: Suspected unexpected serious adverse reactions**

No SUSARs were reported.

**2.5 HEALTH ECONOMIC DATA**

*Participants*

The number of participants allocated to sertraline monotherapy, CBT monotherapy and sertraline plus CBT were 15, 16 and 18 respectively.

*Completion rates*

Complete resource use and EQ-5D-3L data was available throughout the study (at baseline, 16 week and 52 follow up points) for 23 participants (46.9% of participants), as shown in Table 17. Completion rates for the individual healthcare resource use items were fairly consistent; out of those that attempted it only two participants did not answer all of the questions, both failing to provide a response regarding help received from carer, friend/family member, or any other person. To increase the number of participants that could be included within the base-case analysis it was assumed these two participants received no help from a professional carer (this was justified by the fact that no other respondents reported receiving such care).

**Table 18: Questionnaire completion rates - EQ-5D and resource use**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Sertraline monotherapy  [n=15] | | | CBT monotherapy  [n=16] | | | CBT + sertraline  [n=18] | | |
|  | Baseline | Week 16 | **Week 52** | Baseline | Week 16 | **Week 52** | Baseline | Week 16 | **Week 52** |
| EQ-5D | 15 | 7 | **6** | 15 | 9 | **8** | 17 | 13 | **9** |
| Health professionals | 15 | 7 | **6** | 15 | 9 | **8** | 17 | 13 | **9** |
| Hospital admissions | 15 | 7 | **6** | 15 | 9 | **8** | 17 | 13 | **9** |
| Other care services | 15 | 7 | **6** | 15 | 9 | **8** | 17 | 13 | **9** |
| Help from carer, friend or family member | 15 | 7 | **6** | 15 | 9 | **8**\* | 17 | 13 | **9**\* |

\*A total of two participants did not complete this subsection of the resource questionnaire and zero use has been assumed

*Intervention costs*

In Table 19 it can be seen that the mean number of sertraline related appointments that occurred in the 52 week follow up period was greater in the sertraline plus CBT group, compared to sertraline monotherapy, which meant the combined participants also had higher overall mean appointment times. In relation to the average sertraline dosage prescribed, for both groups, this increased from 50mg at week 0 to approaching 200mg by week 8, but deciphering trends after this point was difficult due to fewer participants attending appointments in the latter stages of the study (see Table 19). Mean CBT session attendance and length of appointments were similar for the CBT monotherapy and combined groups (see Table 20). After unit costs (see Table 21) were assigned to these items of resource use, along with the aforementioned supervision and training times, mean annual intervention costs were estimated, where these were substantially lower for the sertraline monotherapy group, followed by CBT monotherapy and the combined group (see Table 22).

**Table 19: Number of sertraline-related appointments attended and mean sertraline dosage prescribed (available case unless stated otherwise, over the 52 week follow up period)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Week number | Sertraline monotherapy [n=15] | | CBT + sertraline [n=18] | |
|  | Number of participants that attended scheduled appointment | Mean sertraline dosage prescribed (mg) | Number of participants that attended scheduled appointment | Mean sertraline dosage prescribed (mg) [n] |
| 0 | 15 | 50.00 [n=15] | 18 | 50.00 [n=18] |
| 2 | 11 | 113.64 [n=11] | 16 | 128.13 [n=16] |
| 4 | 11 | 181.82 [n=11] | 13 | 192.31 [n=13] |
| 8 | 9 | 194.44 [n=9] | 13 | 192.31 [n=13] |
| 16 | 6 | 200.00 [n=6] | 12 | 150.00 [n=12] |
| 24 | 5 | 200.00 [n=5] | 11 | 127.27 [n=11] |
| 32 | 7 | 185.71 [n=7] | 9 | 177.78 [n=9] |
| 52 | 6 | 166.67 [n=6] | 8 | 100.00 [n=8] |
| Mean number of sessions per participant (SD) | 4.67 (2.92) [n=15] | | 5.56 (2.68) [n=18] | |
| Assumed length per session | 30 mins | | 30 mins | |
| Mean hours per participant across 52 weeks (available case) | 2 hours 20 mins [n=15] | | 2 hours 47 mins [n=18] | |
| Mean hours per participant across 52 weeks (complete case) | 3 hours 55 mins [n=6] | | 3 hours 40 mins [n=9] | |

**Table 20: Number of CBT sessions attended (available case unless stated otherwise, over the 52 week follow up period)**

|  |  |  |
| --- | --- | --- |
| Session Number | CBT monotherapy [n=16] | CBT + sertraline [n=18] |
|  | Number of participants that attended each session | |
| Visit 1 | 15 | 14 |
| Visit 2 | 13 | 10 |
| Visit 3 | 13 | 11 |
| Visit 4 | 13 | 11 |
| Visit 5 | 7 | 12 |
| Visit 6 | 10 | 11 |
| Visit 7 | 8 | 12 |
| Visit 8 | 9 | 10 |
| Week 16 | 6 | 8 |
| Week 24 | 5 | 6 |
| Week 32 | 4 | 6 |
| Week 52 | 4 | 5 |
| Mean number of sessions per participant (SD) | 6.69 (4.05) [n=16] | 6.44 (4.68) [n=18] |
| Mean length per session (mins) | 1 hour 41 mins [n=16] | 1 hour 46 mins [n=18] |
| Mean hours per participant across 52 weeks (available case) | 11 hours 13 mins [n=16] | 11 hours 27 mins [n=18] |
| Mean hours per participant across 52 weeks (complete case) | 15 hours 18 mins [n=8] | 15 hours 57 mins [n=9] |

**Table 21: Estimated unit costs, with associated sources**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Resource use | Unit Cost | | | |
| **Sertraline** |  | | | |
| Appointment with specialist registrar | £71.84 6 | | | |
| Supervision (5 minutes per appointment) | £14.88 6 7 | | | |
| Medication monthly prescription (50mg) ± | £2.47 | | | |
| Medication monthly prescription (100mg) ± | £2.52 | | | |
| Medication monthly prescription (150mg) ± | £3.97 | | | |
| Medication monthly prescription (200mg)± | £4.03 | | | |
| **CBT** | Therapist (Band 7) 8 | | Trainer (Band 9) | |
| Therapist (cost per hour of employment) | £52.79 | | £106.71 | |
| **Health Professional contacts (Cost per visit)** | GP Clinic 8 | Home\* 8 | | Hospital 8 |
| Counsellor/ therapist | £50.58 | £62.54 | | £51.98 |
| Mental Health Nurse | £68.04 | £78.71 | | £66.15 |
| Psychologist | £65.00 | £78.87 | | £67.50 |
| Psychiatrist | £150.24 | £193.41 | | £168.60 |
| Nurse (at GP surgery) | £12.12 | N/A | | N/A |
| GP | £31.00 | £63.44 | | £135.27 |
| Physiotherapist | £26.72 | £65.23 | | £48.33 |
| Occupational therapist | £41.83 | £84.66 | | £65.85 |
| Speech therapist | £26.72 | £65.23 | | £27.36 |
| Social worker | £40.45 | £50.01 | | £41.57 |
| GP phone call | £11.85 | | | |
| Nurse phone call | £6.30 | | | |
| **Hospital Admissions (cost per bed day)** | £395.33 9 | | | |
| **Accident and emergency (cost per visit)** | £96.25 9 | | | |
| **Other outpatient visit (cost per visit)** | £116.92 9 | | | |
| **Day case procedure (cost per procedure)** | £398.02 9 | | | |
| **Carer help from family members (one hour home visit)†** | £15.76 10 | | | |

± this includes an additional packaging cost of £1.01, \*includes estimated travel cost, † only included in sensitivity analysis 4 (SA4)

**Table 22: Total intervention costs per participant (available case, total across participants over specified follow up periods)**

|  |  |  |  |
| --- | --- | --- | --- |
| Mean cost per participant | Sertraline monotherapy [n=15] | CBT monotherapy [n=16] | CBT + sertraline [n=18] |
| *Sertraline* |  |  |  |
| Prescribed medication | £26.18 | N/A | £26.75 |
| Appointments (including supervision) | £404.68 | N/A | £476.95 |
| **Total sertraline intervention** | **£430.86** | **N/A** | **£503.70** |
| *CBT* |  |  |  |
| Therapist appointments | N/A | £945.30 | £943.01 |
| Training and Supervision | N/A | £580.71 | £580.68 |
| **Total CBT intervention** | **N/A** | **£1526.01** | **£1523.69** |
| **Total** | **£430.86** | **£1526.01** | **£2027.39** |

*Other NHS and PSS resource use*

Aside from health professional contacts, few other health care services were used and no professional carer input was reported (see Table 23). Moreover, compared to baseline, fewer such contacts were reported to take place at follow-up in the sertraline monotherapy group, but this was not so apparent in the other two groups. Due to the small sample size, these results must be interpreted with caution; for example the high levels of health professional resource use reported within the combined group were due to a small number of individuals (one participant in the combined group reported seeing a counsellor 16 times, and another a GP 10 times, where this also may not have been related to their OCD condition). Where care was reported, participants relied on help from family/friends or any other person; this is a cost not faced by the NHS and has therefore not been included in the base case analysis.

After unit costs (see Table 21) were assigned to these resource items of resource use the mean annual cost for other NHS and PSS costs (see Table 24) can generally be seen to be far outweighed by the intervention cost, particularly for the CBT and combined group. It is also noticeable that other NHS and PSS costs are lower at follow-up for the sertraline monotherapy group, compared to baseline.

**Table 23: Level of resource use (available case, mean per participants over specified time periods)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Sertraline monotherapy | | | CBT monotherapy | | | CBT + sertraline | | |
|  | Baseline†  [n =15] | Week 16  [n=7] | Week 52  [n=6] | Baseline†  [n=15] | Week 16  [n=9] | Week 52  [n=8] | Baseline†  [n=17] | Week 16  [n=13] | Week 52  [n=9] |
| **Healthcare Professional contacts** |  |  |  |  |  |  |  |  |  |
| Counsellor/therapist | 0.07 | 0.57 | 0.00 | 0.07 | 0.56 | 1.00 | 0.24 | 0.00 | 1.78 |
| Mental Health Nurse | 1.00 | 0.00 | 0.00 | 0.20 | 0.22 | 1.38 | 0.59 | 0.77 | 0.67 |
| Psychologist | 0.00 | 0.00 | 0.00 | 0.07 | 0.00 | 0.13 | 0.47 | 0.00 | 0.00 |
| Psychiatrist | 0.33 | 0.00 | 0.00 | 0.33 | 0.22 | 0.00 | 0.12 | 0.00 | 0.11 |
| Nurse (GP) | 0.33 | 0.00 | 0.00 | 0.20 | 0.00 | 0.25 | 0.12 | 0.00 | 0.33 |
| GP | 1.00 | 0.29 | 0.50 | 1.20 | 0.78 | 3.25 | 1.71 | 1.62 | 2.11 |
| Physiotherapist | 0.33 | 0.00 | 0.00 | 0.33 | 0.11 | 0.38 | 0.29 | 0.00 | 0.22 |
| Social Worker | 0.00 | 0.00 | 0.00 | 0.27 | 0.11 | 0.25 | 0.24 | 0.00 | 0.00 |
| Other | 1.07 | 1.00 | 0.67 | 0.40 | 1.00 | 0.13 | 1.41 | 1.08 | 0.44 |
| Telephone Calls | 0.93 | 0.29 | 0.67 | 0.20 | 0.89 | 1.63 | 1.00 | 0.39 | 0.33 |
| **Total** | **5.07** | **2.14** | **1.83** | **3.27** | **3.89** | **8.38** | **6.18** | **3.85** | **6.00** |
| **Hospital Admissions** | 0.87 | 0.00 | 0.00 | 0.07 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **A & E visits** | 0.00 | 0.00 | 0.00 | 0.07 | 0.00 | 0.00 | 0.00 | 0.08 | 0.00 |
| **Day case procedure/outpatient visits** | 0.00 | 0.14 | 0.17 | 0.53 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| **Help from professional carer, number of hours per week** | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00\* | 0.00 | 0.00 | 0.00\* |
| **Other help from family/friends or any other person, hours per week** | 3.67 | 0.08 | 7.97 | 7.29 | 0.06 | 3.77 | 0.00 | 0.00 | 1.56 |

*†* Baseline incorporates resource use from the 16 weeks prior to randomisation; Week 16 incorporates the 16 week post randomisation period; Week 52 incorporates the final 16 weeks of the annual post randomisation period \*Assumed = 0 for two participants where the question was not answered

**Table 24: Total costs (available case, mean cost per patient for each previous 16 week period)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Mean cost per participant | Sertraline monotherapy | | | CBT monotherapy | | | CBT + sertraline | | |
|  | Baseline [n=15] | Week 16 [n=7] | Week 52 [n=6] | Baseline [n=15] | Week 16 [n=9] | Week 52 [n=8] | Baseline [n=17] | Week 16  [n=13] | Week 52  [n=9] |
| Total Healthcare Professional visits | £345.47 | £109.71 | £108.30 | £192.43 | £184.72 | £318.14 | £305.67 | £176.24 | £285.86 |
| Hospital Admissions | £342.62 | £0.00 | £0.00 | £26.36 | £13.45 | £0.00 | £0.00 | £15.52 | £0.00 |
| A & E visits | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £22.41 | £0.00 |
| Day case procedure/outpatient visits | £0.00 | £56.86 | £66.34 | £62.35 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 |
| Help from professional career | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 |
| **Total other NHS costs** | **£688.09** | **£166.57** | **£174.63** | **£294.58** | **£184.72** | **£318.14** | **£305.67** | **£191.76** | **£285.86** |

**Table 25: Mean total costs per participant (complete case, estimated annual mean cost per patient)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Mean total cost per participant | Sertraline monotherapy [n=6] | | | CBT monotherapy [n=8] | | | CBT + sertraline [n=9] | | |
| Sertraline |  | | |  | | |  | | |
| Prescribed medication | £48.95 | | | N/A | | | £38.64 | | |
| Appointments and supervision | £679.29 | | | N/A | | | £626.29 | | |
| **Total sertraline costs** | **£728.24** | | | **N/A** | | | **£664.93** | | |
| CBT |  | | |  | | |  | | |
| Therapist sessions | N/A | | | £1309.21 | | | £1319.85 | | |
| Training and Supervision | N/A | | | £580.71 | | | £580.68 | | |
| **Total CBT intervention cost** | **N/A** | | | **£1889.92** | | | **£1900.53** | | |
|  | Baseline | Week 16 | Week 52 | Baseline | Week 16 | Week 52 | Baseline | Week 16 | Week 52 |
| Healthcare Professional contacts | £371.38 | £118.51 | £250.05 | £164.23 | £207.81 | £646.86 | £456.09 | £190.23 | £583.43 |
| Hospital Admissions | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 |
| A & E visits | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £22.41 | £14.00 |
| Day case procedure/outpatient visits | £0.00 | £66.34 | £149.26 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 |
| Help from professional career | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 | £0.00 |
| **Total other NHS and PSS costs** | **£371.38** | **£184.85** | **£399.31** | **£164.23** | **£207.81** | **£646.86** | **£456.09** | **£212.64** | **£597.43** |
| **Overall annual NHS and PSS cost†** | **£1312.40** | | | **£2744.59** | | | **£3375.54** | | |

*†*excluding resource use at baseline; Baseline incorporates resource use from the previous four months post randomisation; Week 16 incorporates the 16 week post randomisation period; Week 52 incorporates the final 36 weeks of annual follow up post randomisation period

**Table 26: Outcomes (available case, per participant)**

|  |  |  |  |
| --- | --- | --- | --- |
| Item mean score (SD) [n] | Sertraline monotherapy [n=15] | CBT monotherapy [n=16] | CBT + sertraline [n=18] |
| Baseline EQ-5D-3L score | 0.638 (0.363) [n=15] | 0.565 (0.435) [n=15] | 0.514 (0.322) [n=17] |
| 16 week EQ-5D-3L score | 0.858 (0.104) [n=7] | 0.790 (0.248) [n=9] | 0.732 (0.236) [n=13] |
| 52 week EQ-5D-3L score | 0.831 (0.248) [n=6] | 0.609 (0.443) [n=8] | 0.724 (0.255) [n=9] |
| EQ-5D-3L 16 week change score | 0.210 (0.361) [n=7] | 0.124 (0.261) [n=9] | 0.246 (0.273) [n=13] |
| EQ-5D-3L 52 week change score | 0.189 (0.459) [n=6] | -0.016 (0.147) [n=8] | 0.205 (0.240) [n=9] |
| **QALY score (over 52 weeks)** | **0.820 (0.172) [n=6]** | **0.689 (0.319) [n=8]** | **0.691 (0.204) [n=9]** |

n=Number for whom data were available; SD=standard deviation; QALY=Quality Adjusted Life Years

*Outcomes*

Table 26 summarises the EQ-5D-3L and QALY scores of participants that completed the questionnaire at baseline, 16 and 52 weeks. Over the 52 week follow-up period, for those with baseline and 52 week data, the mean EQ-5D-3L increase was positive for both the sertraline monotherapy and combined group, but negative within the CBT monotherapy group (0.189, 0.205 and -0.016 respectively). For all groups the EQ-5D-3L change was greater within the first 16 weeks than at the 52 week point.

The overall annual cost to the NHS and PSS, based on the summation of the intervention and other NHS costs for those with complete data, are presented in Table 25. It is apparent that the mean intervention cost for all three groups outweighs the total other NHS and PSS costs, where this was particularly the case for both CBT groups where the intervention costs are more than double the total other NHS and PSS costs. Moreover, healthcare professional contact costs are by far the largest cost driver within this latter cost category.

The results of the base-case bivariate regression are shown in Table 26. Compared to both other treatment options, sertraline monotherapy was on average both less costly and more effective. Based on these mean estimates alone sertraline monotherapy would be estimated to be dominant and cost-effective. However, there was still some associated uncertainty (there was estimated to be a >5% chance of making the wrong decision by choosing sertraline monotherapy, based on the cost-effectiveness acceptability curve at a threshold value of £20,000 per QALY).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Table 27: Estimates of incremental cost, incremental effect and net monetary benefit and sensitivity analysis for sertraline monotherapy compared to CBT monotherapy and combination therapy** | | | | | | |
| Analysis |  | incremental cost (95% CI) | incremental effect (95% CI) | Incremental cost effectiveness ratio (ICER) | Probability of being cost effective±  Sertraline monotherapy, CBT monotherapy, combination | |
|  |  | QALY gain |  |  | |
| Base-case: complete case | Sertraline Monotherapy vs CBT monotherapy (6,8) | -£1328.57  (-2101.76 to -£555.39) | 0.1823  (0.0447 to 0.3199) | Dominant | Sertraline  CBT  Combination | 94.7%  2.0%  3.3% |
| Sertraline Monotherapy vs  CBT + sertraline (6,9) | -£2175.70  (-£2966.26 to -£1385.13) | 0.1135  (-0.0290 to 0.2560) | Dominant |
| SA1: excluding intervention training | Sertraline Monotherapy vs CBT monotherapy (6,8) | -£747.86  (-£1521.05 to £25.32) | 0.1823  (0.0447 to 0.3199) | Dominant | Sertraline  CBT  Combination | 92.4%  2.5%  5.1% |
| Sertraline Monotherapy vs  CBT + sertraline (6,9) | -£1595.01  (-£2385.58 to -£804.45) | 0.1135  (-0.0290 to 0.2560) | Dominant |
| SA2: multiple imputation | Sertraline Monotherapy vs CBT monotherapy (15,16) | -£681.34  (-£1566.13 to £203.45) | 0.0475  (-0.0940 to 0.1890) | Dominant | Sertraline  CBT  Combination | 100%  0%  0% |
| Sertraline Monotherapy vs  CBT + sertraline (15,18) | -£1196.53  (-£2077.25 to -£315.79) | 0.0045  (-0.1340 to 0.1430) | Dominant |
| SA3: including carer costs (paid for privately) plus any other help/care | Sertraline Monotherapy vs CBT monotherapy (6,8) | £2388.53  (-£680.91 to £5457.97) | 0.1834  (0.0457 to 0.3210) | £13,026 | Sertraline  CBT  Combination | 67.7%  28.9%  3.4% |
| Sertraline Monotherapy vs  CBT + sertraline (6,9) | -£1674.46  (-£4812.90 to £1463.98) | 0.1177  (-0.0249 to 0.2603) | Dominant |

95% CI=95% confidence interval; SA1…SA4 refer to the different sensitivity analyses described in the Methods; QALY= Quality Adjusted Life Years over 52 weeks; ±probability of being cost-effective on the cost-effectiveness acceptability curve (CEAC) at the threshold (λ) of £20,000 per QALY

1. (M&D) PaCC. Pay award for hospital medical and dental staff, doctors and dentists in public health, the community health service and salaried primary dental care. 2016.  
2. Health and Social Care Information Centre. Prescription Cost Analysis: England 2015. 2016.  
3. Curtis L, Burns A. Unit Costs of Health and Social Care 2016. University of Kent: 2016.  
4. Health Do. NHS reference costs 2015 to 2016. <https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016:> 2016.  
5. Office for National Statistics (ONS). Annual Survey of Hours and Earnings (ASHE). Accessed at: <http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/guide-method/method-quality/specific/labour-market/annual-survey-of-hours-and-earnings/index.html>, 2015.

*Sensitivity Analysis*

Compared to the other two treatment options, sertraline monotherapy was estimated to be more effective in terms of mean QALY gain in each of the three sensitivity analyses (see Table 27). For the first two sensitivity analyses sertraline monotherapy was also estimated to be associated with lower mean costs, and would thereby be estimated to dominate the two other treatment options. In the third sensitivity analysis, where a cost for other help from family/friends or any other person was also included sertraline monotherapy estimated to be more costly than CBT monotherapy, but still associated with an ICER below the £20,000 per QALY value. Accordingly, in line with the base-case results, sertraline monotherapy was estimated to be cost-effective, compared to the other two treatment options, in each of the three sensitivity analyses. Similarly, the probability of making the wrong decision by choosing a particular option was always <35% according to the CEAC (at an (λ) of £20,000 per QALY).

**3.0 DISCUSSION**

Several interventions are available for treating OCD. Few studies, however, have compared the relative effectiveness of these interventions in a single analysis. In addition, given the chronic and relapsing nature of OCD, there has been insufficient study of the longer-term treatment outcomes under controlled conditions. To this end, Skapinakis and colleagues recently performed a systematic review and network meta-analysis, comparing all available treatments for adults with OCD using both direct and indirect data27. Fifty four trials (6652 participants) were included in the network meta-analysis. A shortage of studies comparing active psychological therapy with psychological placebo was noted. The results showed that cognitive-behavioural forms of psychotherapy as well as clomipramine and SSRI (as a class) produced greater improvement in clinical ratings than did pill-placebo. Psychotherapy interventions were reported to be associated with a greater effect than medication, but it was also noted that in most psychotherapy trials, patients who were taking stable doses of antidepressants were not excluded from the psychotherapy arms. Thus, there was considerable uncertainty about relative effectiveness. The analysis concluded that the combination of behavioural forms of psychotherapy with medications is probably more effective than either monotherapy, at least in the management of severe OCD, and that pragmatic trials with improved research design are needed to establish the differential efficacy between psychotherapies and medications with greater certainty.

The existing uncertainty is of major relevance for health service planning, since NICE guidelines currently recommend either CBT or SSRI monotherapy as first line approaches, reserving combination treatment for patients with more severe or resistant OCD28. Moreover, in countries such as the UK, CBT is commonly provided for a range of psychiatric disorders including OCD, being delivered in non-medical psychological therapy service settings, such as the UK Improving Access to Psychological Therapies programme ([*https://www.england.nhs.uk/mental-health/adults/iapt/*](https://www.england.nhs.uk/mental-health/adults/iapt/)*),* where medicines management is not always available.

The findings of this feasibility study underline this uncertainty, so emphasising the need for a definitive study, and also suggest that running such a study is likely to be feasible and acceptable to patients.

***Feasibility***

Recruitment was acceptable across the study centres, with secondary mental health care services acting as the principal referral route. Retention to week 8 was also acceptable across all the study arms. Although retention in the combined arm remained good to Week 16, a sizeable number of withdrawals occurred after 8 weeks in both the monotherapy groups, suggesting a possible advantage in terms of retention for combined treatment, at least in the acute phase. To maximise the number of evaluable cases, factoring in the unplanned delays related to starting CBT, future studies may aim for a slightly earlier primary endpoint, around 12 weeks. After 16 weeks, fewer patients discontinued and the majority of the patients who had reached week 16 remained in the study until the 52 week endpoint, suggesting long-term follow-up is feasible for those patients reaching the end of acute phase treatment.

Study treatment was generally well tolerated and adhered to by the majority of patients. However, four patients randomised to receive sertraline either reduced or stopped it, while another four not randomised to sertraline procured a SSRI prescription from their GP. When questioned, several patients explained that they had found randomisation difficult.

Eleven of a total of 239 adverse events were considered to be ‘severe’. One patient receiving sertraline attempted suicide, emphasising the importance of caution in the assessment of suicide risk in OCD patients. No specific association has so far been reported in the scientific literature between the use of SSRI and suicidal acts in adults with OCD. However, an observational cohort study of patients with depression29 reported increased rates of suicidal behaviour in the first 28 days of starting and stopping antidepressants, highlighting the need for careful monitoring of patients receiving SSRI during these periods.

***Effectiveness***

As the number of patients completing 16 weeks fell short of the study power set in the protocol, the findings are subject to type I error and we cannot be confident that the observed effect is reliable. Therefore caution is required when interpreting the study outcomes. Notwithstanding, CBT fell considerably short of SSRI in terms of clinical and cost effectiveness on the observed case analyses, emphasising the persisting need for a definitive study. On the primary Y-BOCS analysis, at the primary week 16 endpoint, patients receiving CBT were responding less well than those receiving sertraline (Cohen’s *d* =.27) or sertraline in combination with CBT (Cohen’s *d*= .39), suggesting that the combined treatment arm may offer the most clinically effective treatment, especially over CBT monotherapy. These findings align with those from two small historic placebo-controlled studies in adults with OCD, one published by Hohagen et al.30, in which SSRI combined with multimodal behaviour therapy outperformed the psychological therapy given alone on a number of clinical outcomes measures including obsessions and depression, and one published by Cottraux et al.31 in which fluvoxamine and exposure therapy were synergistic, with an advantage for combined treatment over exposure therapy on rituals at week 8 and on depression at week 24.

If substantiated in a larger trial, our finding of superior effectiveness for sertraline, either in combination with CBT or as a monotherapy, would cast question on the existing evidence-based treatment guidelines (e.g. 32) that tend to recommend CBT or SSRI monotherapy as equivalent first line treatments. Moreover, the finding that combination treatment may be the most efficacious in this study sample, at least in the short term (up to 16 weeks), would suggest that combination treatment should not necessarily be reserved for the most severe and treatment resistant patients.

Beyond week 16, falling retention across all groups made interpretation exceedingly difficult. However, the advantages of combination therapy were not sustained. Sertraline monotherapy showed the greatest improvement in the Y-BOCS at week 32 and week 52, out-performing both CBT monotherapy with a large effect size (Cohen’s *d* = .57, .56 respectively) and also out-performing combination treatment (Cohen’s *d* = .49, .44 respectively).

The failure of combined treatment to show a sustained advantage beyond 16 weeks is, on the face of it, difficult to explain. The gains seen for CBT monotherapy after 16 weeks were slight, but those for SSRI monotherapy were more robust: suggesting that combination with CBT may somehow interfere with the effect of SSRI treatment. Of note, the mean prescribed sertraline dose was rather low overall, considering 200mg/day is accepted as the optimal dose, which may have reduced efficacy in both the sertraline monotherapy and combined treatment arms. However, this was more noticeable in the combined arm, suggesting patients receiving CBT may have experienced even more difficulties in taking sertraline at optimised doses. This could provide an explanation as to why they failed to improve to the same extent as their monotherapy counterparts. In the combination arm, patients and their clinicians may have biased the focus of treatment toward the adjunctive CBT and held back from taking the maximum sertraline dose. The possibility that a negative interaction exists between receiving CBT and medication should be investigated in more depth, as this would have important treatment implications. Perhaps also some of the gains associated with the combination arm depended upon non-specific therapist effects that were missed after 16 weeks, when regular contact with the CBT therapist came to an end. Clarification of these factors should be pursued through quantitative and qualitative analysis in the substantive study.

The secondary clinical outcomes largely aligned with the Y-BOCS data, providing a degree of convergent validity to the findings. Specifically, changes in the clinical global severity and improvement scores and the SDS largely mirrored the Y-BOCS data, at least up to Week 16, with numerical advantages seen for the combined treatment and SSRI arms over CBT. In the case of the SDS, after 16 weeks the advantages of combined treatment waned and by Week 52, sertraline showed the greatest improvement and CBT the least.

Sertraline monotherapy produced the most beneficial effect on depressive symptoms, with the mean baseline MADRS improving by 50% as early as 8 weeks of treatment. In contrast, CBT was associated with no improvement in depressive symptoms: mean MADRS scores at both endpoints were numerically higher than at baseline. This finding runs contrary to a large meta-analysis study of Anxiety Disorders and OCD33, which found that CBT significantly reduced depression in patients with OCD (Hofmann and Smits, 2008). Perhaps by adhering strictly to the exposure and response prevention model, patients receiving CBT experienced greater levels of distress that manifested as increased MADRS scores. This may also explain the relatively reduced ‘antidepressant’ effect when sertraline was combined with CBT, compared with sertraline monotherapy.

*Health Economic Findings*

As a feasibility study, designed to inform the design of any subsequent more definitive study, it is notable that total other NHS and PSS costs were estimated to be markedly outweighed by the intervention costs in all three groups, and that within this cost category health professional contacts were by far the main cost driver. Accordingly, resource items such as professional carer time and A&E visits would seem unlikely to have a notable change in any future study and there is therefore an argument that these need not be measured as it would reduce patient burden. In turn this may improve response rates were lower than expected, possibly due to the requirement for in-person follow-up, and actions to rectify this should be investigated.

Sertraline monotherapy was estimated to be associated with both a higher mean QALY gain and lower mean costs, compared to both CBT monotherapy and Sertraline plus CBT. However, these preliminary cost effectiveness results had associated uncertainty and should be treated with caution due to the relatively small sample size. That said, were they to be replicated in a more definitive study then there would be potential for large cost savings to the NHS as Sertraline monotherapy would be associated with lower costs than current usual care.

Less than half the participants completed both the EQ-5D and resource use questionnaires at 16 and 52 weeks post randomisation. As such it is possible these participants could be a biased group and not representative of all recruited participants. Accordingly, these results need to be treated with caution. However, were the findings to be replicated in a more definitive study there is the potential for substantial cost savings to the NHS as sertraline monotherapy does not currently constitute treatment as usual for this population.

We are aware of two previous publications 11 which have looked at the cost-effectiveness of cognitive behavioural therapy within OCD patients compared with SSRIs (selective serotonin reuptake inhibitors) (at a class level including sertraline). Skapinakis et al. 11 developed a probabilistic model using the results of a network meta-analysis to estimate the costs and benefits associated with the independent use of cognitive behavioural therapy, SSRI, and a combination of fluvoxamine (an SSRI) and CBT, over a five year time horizon within adults, where only the cost of intervention medication and therapy was included. In keeping with our results, the independent use of SSRIs was estimated to be the lowest cost option (£5788), compared to CBT (£7428) and SSRI plus CBT (£7206), where Skapinakis attributed the higher cost of CBT to the relatively higher intensity of the intervention. Despite estimating that the independent use of SSRIs had a smaller QALY gain (3.208), compared to CBT (3.238) and SSRI plus CBT (3.219), they similarly estimated that SSRI was the most cost-effective option (it had the highest net benefit at a £20,000 per QALY value).

NICE (2006) conducted a meta-analysis to calculate the overall cost of a 12-month course of CBT and SSRIs within OCD patients (based on 10 studies), used both in conjunction and independently. The cost per case from the use of SSRI independently was reported to be £289, whilst for CBT and SSRI plus CBT it was £1,056 and £1,345, respectively. Based on assumed levels of effectiveness, which were informed by relevant literature, the combined option was found to be the most cost-effective, despite having a higher cost. Though the lower SSRI cost is in keeping with our results it is difficult to make direct comparisons with our study as the assumptions on which the costs were based e.g. therapy frequency and session length were not explicitly stated and the mean cost and outcomes of all SSRI treatments were estimated at a class level in the meta-analysis (the effects of e.g. sertraline were not reported separately).

**4.0 CONCLUSIONS**

Recruitment was feasible across three study arms in three centres and the study procedures were acceptable to the majority of patients. Retention was acceptable across the three study arms to Week 8, and in the combined arm to Week16. To maximise the number of evaluable cases, future studies may aim for a primary endpoint around 12 weeks.

Longer term participant retention was adequate, with the majority of those who had reached week 16 remaining in the study until the 52 week endpoint, suggesting long-term follow-up is feasible for those patients reaching the end of acute phase treatment.

At weeks 8 and 16, sertraline treated patients responded better than those receiving CBT in the observed case analyses. The combined arm appeared to offer the most clinically effective treatment (especially over CBT) in the acute treatment phase. Beyond Week 16, falling retention made interpretation difficult, but several analyses including a preliminary health economic analysis suggested there were ongoing advantages for receiving sertraline relative to CBT.

**Implications**

Were these findings to be substantiated in a more definitive study, i.e. if sertraline monotherapy were to be associated with greater sustained efficacy and lower costs than usual care with CBT, there would be the potential for changes to existing treatment guidelines with resulting large cost savings to the NHS. Further research would therefore be of value: our study confirms that a definitive study can and should be conducted.

**REFERENCES**

1. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Archives of general psychiatry 1989;**46**(11):1006-11.

2. Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. International clinical psychopharmacology 1996;**11 Suppl 3**:89-95.

3. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. The British journal of psychiatry : the journal of mental science 1979;**134**:382-9.

4. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA : the journal of the American Medical Association 2001;**285**(15):1987-91.

5. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. International journal of surgery (London, England) 2012;**10**(1):28-55.

6. Brooks R. EuroQol: the current state of play. Health Policy 1996;**37**:53-72.

7. Beecham J, Knapp M. Costing psychiatric interventions. In: Thornicroft G, Brewin C, Wing J (editors). Measuring mental health needs. London: Gaskell, 1992.

8. Curtis L. Unit costs of health and social care.: The University of Kent: Personal Social Services Research Unit, 2009.

9. NICE. Guide to the methods of technology appraisal 2013. National Institute of Health and Clinical Excellence (NICE) publications, 2013.

10. Dolan P. Modelling valuations for EuroQol health states. Med Care 1997;**35**:1095-108.

11. Richardson G, Manca A. Calculation of quality adjusted life years in the published literature: a review of methodology and transparency. Health Econ 2004;**13**:1203–10.

12. O'Hagan A, McCabe C, Akehurst R, et al. Incorporation of uncertainty in health economic modelling studies. Pharmacoeconomics 2005;**23**(6):529-36.

13. (M&D) PaCC. Pay award for hospital medical and dental staff, doctors and dentists in public health, the community health service and salaried primary dental care. 2016.

14. Authority NHSBS. Preface: amendments to the Drug Tariff June 2017. National Health Service Business Authority 2017.

15. Health and Social Care Information Centre. Prescription Cost Analysis: England 2015. 2016.

16. Health Do. NHS reference costs 2015 to 2016. https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016: 2016.

17. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes (4th edition). New York: Oxford University Press, 2015.

18. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ. 2005;14:487-96.

19. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. J Health Econ. 1999;18(3):341-64.

20. Briggs AH, Clark T, Wolstenholme J, Clarke P. Missing...presumed at random: cost-analysis of incomplete data. Health Econ. 2003;12:377-92.

21. Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. Health Econ. 2004;14:461-75.

22. Briggs AH, O'Brien BJ, Blackhouse G. Thinking outside the box: recent advances in the analysis and presentation of uncertainty in cost-effectiveness studies. Annu Rev Public Health. 2002;23:377-401.

23. Royston P. Multiple imputation of missing values: update of ice. Stata Journal. 2005:527-36.

24. Little RJA, Rubin DB. Statistical analysis with missing data (2nd edition). Hoboken, New Jersey: Wiley, 2002.

25. Office for National Statistics (ONS). Annual Survey of Hours and Earnings (ASHE). Accessed at: <http://webarchive.nationalarchives.gov.uk/20160105160709/http://www.ons.gov.uk/ons/guide-method/method-quality/specific/labour-market/annual-survey-of-hours-and-earnings/index.html>, 2015.

26. Mallinckrod CH, Lane PW, Schnell D, Yahong Peng, Mancuso, JP. (2008) Recommendations for the Primary Analysis of Continuous Endpoints in Longitudinal Clinical Trials. Therapeutic Innovation & Regulatory Science. 42(4), p303-319.

27. Skapinakis P, Caldwell D, Hollingworth W, Bryden P, Fineberg N, Salkovskis P, et al. A systematic review of the clinical effectiveness and cost-effectiveness of pharmacological and psychological interventions for the management of obsessive–compulsive disorder in children/adolescents and adults. Health Technol Assess 2016;20(43).

28. National Collaborating Centre for Mental Health (2006). Obsessive-Compulsive Disorder: Core Interventions in the Treatment of Obsessive-Compulsive Disorder and Body Dysmorphic Disorder. Leicester (UK): British Psychological Society. Available from: https://[www.ncbi.nlm.nih.gov/books/NBK56458/](http://www.ncbi.nlm.nih.gov/books/NBK56458/)

29. Coupland C, Hill T, Morriss R, Arthur A, Moore M, Hippisley-Cox J. (2015). Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database. *BMJ* **350**:h517. Available from doi:10.1136/bmj.h517

30. Hohagen F, Winkelmann G, Rasche-Rüchle H, Hand I, König A, Münchau N, Hiss H, Geiger-Kabisch C, Käppler C, Schramm P, Rey E, Aldenhoff J, Berger M. (1998). Combination of behaviour therapy with fluvoxamine in comparison with behaviour therapy and placebo. Results of a multicentre study. *Br J Psychiatry Suppl* (35):71-8. Available from PMID:9829029

31. Cottraux J, Mollard E, Bouvard M, Marks I. (1993). Exposure therapy, fluvoxamine, or combination treatment in obsessive-compulsive disorder: one-year followup. *Psychiatry Res* **49**(1):63-75. Available from doi: 10.1016/0165-1787(93)90030-K

32. National Institute for Health and Care Excellence (2006). *Obsessive compulsive disorder: Core interventions in the treatment of obsessive-compulsive disorder and body dysmorphic disorder.***APPENDICES**

**Appendix A: Breakdown by Centre**

**Table 4a HPFT – Patient Baseline Data**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | N | All | Randomised/Study Arm | | | | | |
| n | Sertraline | n | CBT | n | Combined |
| Age | 24 | 30.4 (9.6) | 8 | 31.8 (10.0) | 8 | 29.9 (9.7) | 8 | 29.5 (10.1) |
| Y-BOCS | 24 | 26.7 (5.3) | 8 | 28.3 (4.5) | 8 | 24.4 (5.7) | 8 | 27.4 (5.6) |
| CGI Severity | 23 | 4.2 (0.7) | 7 | 4.4 (1.0) | 8 | 3.9 (0.6) | 8 | 4.3 (0.5) |
| SDS | 21 | 17.9 (5.0) | 6 | 22.3 (3.4) | 8 | 15 (2.7) | 7 | 17.3 (5.8) |
| Autism Quotient | 23 | 20.8 (6.6) | 8 | 20 (6.1) | 8 | 21.4 (6.3) | 7 | 21.1 (8.2) |
| MADRS | 24 | 14.8 (7.7) | 8 | 18 (9.5) | 8 | 12 (6.5) | 8 | 14.4 (6.6) |
| EQ5D |  |  |  |  |  |  |  |  |
| Health Score | 23 | 58.8 (20.8) | 8 | 56.4 (20.5) | 8 | 55.9 (19.5) | 7 | 64.9 (24.2) |
| CANTAB |  |  |  |  |  |  |  |  |
| Stop-Signal | 23 | 216 (64.2) | 8 | 256.3 (53.2) | 8 | 205.5 (60) | 7 | 181.9 (62.7) |
| ID-ED | 23 | 38.8 (37.6) | 8 | 39.6 (58.9) | 8 | 31.6 (21.6) | 7 | 46.1 (21.6) |
| Go-no-go | 17 | 442.5 (86.6) | 6 | 411.5 (105.7) | 7 | 461.8 (85.8) | 4 | 455.4 (60) |
| Gamble Task | 23 | 0.5 (0.1) | 8 | 0.6 (0.1) | 8 | 0.5 (0.1) | 7 | 0.6 (0.2) |

**Table 4b- SHTN - Patient Baseline Data**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | N | All | Randomised/Study Arm | | | | | |
| n | Sertraline | n | CBT | n | Combined |
| Age | 17 | 36.2 (15.4) | 5 | 39 (21.0) | 5 | 38.6 (16.0) | 7 | 32.6 (11.8) |
| Y-BOCS | 17 | 27.6 (7.2) | 5 | 25.8 (7.6) | 5 | 32 (8.4) | 7 | 25.9 (5.5) |
| CGI Severity | 17 | 4.8 (1) | 5 | 4.6 (0.9) | 5 | 5.2 (1.1) | 7 | 4.6 (1) |
| SDS | 16 | 19.8 (8.8) | 5 | 14.6 (12.1) | 4 | 22.6 (6.8) | 7 | 21.9 (6.3) |
| Autism Quotient | 17 | 23.5 (5.6) | 5 | 25.6 (3.6) | 5 | 21.8 (7.3) | 7 | 23.3 (5.7) |
| MADRS | 17 | 21.5 (10.6) | 5 | 16.2 (10.9) | 5 | 21 (9.4) | 7 | 25.7 (10.9) |
| EQ5D |  |  |  |  |  |  |  |  |
| Health Score | 16 | 46.6 (32.9) | 4 | 59 (34.5) | 5 | 33.8 (36.1) | 7 | 48.6 (31.5) |
| CANTAB |  |  |  |  |  |  |  |  |
| Stop-Signal | 15 | 255.4 (165) | 4 | 213.7 (30.1) | 4 | 378.9 (277.7) | 7 | 208.6 (103.1) |
| ID-ED | 15 | 45.4 (46.7) | 4 | 52 (81.4) | 4 | 70.8 (28.4) | 7 | 27.1 (23) |
| Go-no-go | 12 | 554.5 (141.1) | 3 | 562.3 (133.1) | 4 | 666.5 (155.5) | 5 | 460.2 (63.9) |
| Gamble Task | 15 | 0.6 (0.2) | 4 | 0.5 (0.3) | 4 | 0.6 (0.2) | 7 | 0.6 (0.1) |

**Table 4c – SWSG - Patient Baseline Data**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | N | All | Randomised/Study Arm | | | | | |
| n | Sertraline | n | CBT | n | Combined |
| Age | 8 | 38.8 (15.3) | 2 | 28.5 (6.4) | 3 | 39.3 (17.0) | 3 | 45 (18.7) |
| Y-BOCS | 8 | 25.8 (5.1) | 2 | 24.5 (0.7) | 3 | 23.7 (4) | 3 | 28.7 (7.4) |
| CGI Severity | 8 | 4 (1.3) | 2 | 4 (-) | 3 | 3.3 (0.6) | 3 | 4.7 (2.1) |
| SDS | 7 | 14.3 (7.2) | 2 | 16.5 (2.1) | 2 | 8.5 (10.6) | 3 | 16.7 (7.1) |
| Autism Quotient | 7 | 20.4 (4.2) | 2 | 24 (1.4) | 2 | 17.5 (2.1) | 3 | 20 (5.3) |
| MADRS | 8 | 8.3 (9.7) | 2 | 9 (9.9) | 3 | 1 (1) | 3 | 15 (11.5) |
| EQ5D |  |  |  |  |  |  |  |  |
| Health Score | 7 | 67.1 (14.1) | 2 | 67.5 (10.6) | 2 | 67.5 (24.7) | 3 | 66.7 (15.3) |
| CANTAB |  |  |  |  |  |  |  |  |
| Stop-Signal | 6 | 206.4 (48.2) | 2 | 187 (52.8) | 1 | 179 (-) | 3 | 228.5 (54.2) |
| ID-ED | 6 | 42.2 (21.9) | 2 | 40 (35.4) | 1 | 66 (-) | 3 | 35.7 (15) |
| Go-no-go | 5 | 534.6 (55.9) | 1 | 488.2 (-) | 1 | 490.3 (-) | 3 | 564.8 (53.1) |
| Gamble Task | 6 | 0.7 (0.1) | 2 | 0.7 (0.1) | 1 | 0.4 (-) | 3 | 0.8 (0.05) |

**Table 7a: Centre HPFT, patient progression through study protocol following randomization**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | n | Study arm | | |
| Sertraline | CBT | Combined |
| **Randomised** | 24 | 8 | 8 | 8 |
| Did not receive allocated treatment | 4 | 1 | 0 | 3 |
| *Did not want CBT* |  | 0 | 0 | 0 |
| *Did not want drug* |  | 1 | 0 | 1 |
| *Other* |  | 0 | 0 | 2 |
| Received allocated treatment | 20 | 7 | 8 | 5 |
|  |  |  |  |  |
| **8 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 1 | 0 | 0 |
| Withdrawn from study |  | 2 | 0 | 3 |
| Other |  | 1 | 1 | 0 |
| Excluded from Analysis | 8 | 4 | 1 | 3 |
| Discontinued treatment |  | 0 | 0 | 1 |
| Analysed | 16 | 4 | 7 | 5 |
|  |  |  |  |  |
| **16 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 1 | 0 | 0 |
| Withdrawn from study |  | 2 | 1 | 3 |
| Other |  | 1 | 2 | 0 |
| Excluded from Analysis | 10 | 4 | 3 | 3 |
| Discontinued treatment |  | 0 | 2 | 1 |
| Analysed | 14 | 4 | 5 | 5 |
|  |  |  |  |  |
| **32 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 1 | 1 | 0 |
| Withdrawn from study |  | 4 | 2 | 4 |
| Other |  | 0 | 0 | 0 |
| Excluded from analysis | 12 | 5 | 3 | 4 |
| Discontinued treatment |  | 0 | 3 | 1 |
| Analysed | 12 | 3 | 5 | 4 |
|  |  |  |  |  |
| **52 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 1 | 2 | 0 |
| Withdrawn from study |  | 4 | 2 | 4 |
| Other |  | 0 | 0 | 0 |
| Excluded from analysis | 13 | 5 | 4 | 4 |
| Discontinued treatment |  | 0 | 3 | 1 |
| Analysed | 11 | 3 | 4 | 4 |
|  |  |  |  |  |
| Completed the study | 7 | 3 | 1 | 3 |

**Table 7b: Centre SHTN, patient progression through study protocol following randomization**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | n | Study arm | | |
| Sertraline | CBT | Combined |
| **Randomised** | 17 | 5 | 5 | 7 |
| Did not receive allocated treatment |  |  |  |  |
| *Did not want CBT* |  |  |  |  |
| *Did not want drug* |  |  |  |  |
| *Other* |  |  |  |  |
| Received allocated treatment | 17 | 5 | 5 | 7 |
|  |  |  |  |  |
| **8 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 0 | 0 | 0 |
| Withdrawn from study |  | 1 | 0 | 0 |
| Other |  | 0 | 2 | 1 |
| Excluded from Analysis | 4 | 1 | 2 | 1 |
| Discontinued treatment |  | 0 | 0 | 1 |
| Analysed | 13 | 4 | 3 | 6 |
|  |  |  |  |  |
| **16 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 0 | 1 | 0 |
| Withdrawn from study |  | 1 | 1 | 1 |
| Other |  | 1 | 0 | 1 |
| Excluded from Analysis | 6 | 2 | 2 | 2 |
| Discontinued treatment |  | 0 | 1 | 2 |
| Analysed | 11 | 3 | 3 | 5 |
|  |  |  |  |  |
| **32 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 1 | 1 | 0 |
| Withdrawn from study |  | 1 | 1 | 3 |
| Other |  | 0 | 1 | 1 |
| Excluded from analysis | 9 | 2 | 3 | 4 |
| Discontinued treatment |  | 0 | 1 | 3 |
| Analysed | 8 | 3 | 2 | 3 |
|  |  |  |  |  |
| **52 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 1 | 1 | 0 |
| Withdrawn from study |  | 1 | 1 | 3 |
| Other |  | 0 | 0 | 0 |
| Excluded from analysis | 7 | 2 | 2 | 3 |
| Discontinued treatment |  | 0 | 2 | 3 |
| Analysed | 10 | 3 | 3 | 4 |
|  |  |  |  |  |
| Completed the study | 5 | 3 | 1 | 1 |

**Table 7c: Centre SWSG, patient progression through study protocol following randomization**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **SWSG** | n | Study arm | | |
| Sertraline | CBT | Combined |
| **Randomised** | 8 | 2 | 3 | 3 |
| Did not receive allocated treatment | 1 |  | 1 |  |
| *Did not want CBT* |  |  |  |  |
| *Did not want drug* |  |  |  |  |
| *Other* |  |  | 1 |  |
| Received allocated treatment | 7 | 2 | 2 | 3 |
|  |  |  |  |  |
| **8 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 0 | 0 | 0 |
| Withdrawn from study |  | 0 | 1 | 0 |
| Other |  | 1 | 0 | 0 |
| Excluded from Analysis | 2 | 1 | 1 | 0 |
| Discontinued treatment |  | 0 | 0 | 1 |
| Analysed | 6 | 1 | 2 | 3 |
|  |  |  |  |  |
| **16 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 0 | 0 | 0 |
| Withdrawn from study |  | 1 | 1 | 0 |
| Other |  | 1 | 1 | 0 |
| Excluded from Analysis | 4 | 2 | 2 | 0 |
| Discontinued treatment |  | 0 | 0 | 1 |
| Analysed | 4 | 0 | 1 | 3 |
|  |  |  |  |  |
| **32 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 1 | 1 | 0 |
| Withdrawn from study |  | 1 | 1 | 2 |
| Other |  | 0 | 0 | 0 |
| Excluded from analysis | 6 | 2 | 2 | 2 |
| Discontinued treatment |  | 0 | 0 | 0 |
| Analysed | 2 | 0 | 1 | 1 |
|  |  |  |  |  |
| **52 Week Follow-up** |  |  |  |  |
| Lost to follow up |  | 1 | 1 | 0 |
| Withdrawn from study |  | 1 | 1 | 2 |
| Other |  | 0 | 0 | 0 |
| Excluded from analysis | 6 | 2 | 2 | 2 |
| Discontinued treatment |  | 0 | 0 | 0 |
| Analysed | 2 | 0 | 1 | 1 |
|  |  |  |  |  |
| Completed the study | 2 | 0 | 1 | 1 |

**Appendix B: Review of Audio Files, Dr Lynne Drummond**

**Date of Review: 12th May 2017**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **PID** | **Session** | **File Reviewed y/n** | **Compliance rating score** | **Comments** |
| SHTN831 | 1 | Y | 7 | Taking History, Goal setting of aims. CSA @ age 11yrs following development of OCD, explanation of ERP |
| SHTN362 | 1 | Y | 7 | First session with patient, very chatty patient and difficult to control but therapist handled her well. Public toilet-urine on seat, said she would go to another toilet |
| SWSG377 | 4 | Y | 6 | ERP session, ‘safety behaviour’ good reinforcement, then started to go back on herself. Then started ERP session. 30 mins exposure. |
| HPFT350 | 2 | N/A | N/A | Corrupted File |
| SWSG064 | 1 | Y | 6 | First 13 minutes all about cancellation. Therapist leaves patient alone at 1 hr. Very slow explanation. |
| SWSG075 | 4 | Y | 8 | Patient had been mostly doing RP and resisting exposure. Therapist addressing this with specific instructions. Good compliance with protocol |
| HPFT824 | 3 | Y | 6 | Problem sleeping, good reinforcement, reviewed homework over 8 minutes, started ERP @ 50mins. |
| SHTN891 | 2 | Y | 6 | Lady with health anxiety, believes he has a brain tumour/heart attack. No reassurance and cognitive work. |
| SHTN154 | 2 | Y | 4 | Stopped Sertraline recently, still collecting history, Education after 1 hr, cognitive therapy +++++ |
| HPFT489 | 4 | Y | 7 | Reviewed for 18 mins + started ERP 21mins |

1. Completion will be defined differently according to the particular outcome being considered. Patient completion is more complex to define, but completion of outcome measures depends on the presence of absence of completed data for each measure (see table 12 Scale Characteristics) [↑](#footnote-ref-2)