



## Clinical trial results:

**A Phase IV randomised controlled trial of the selective serotonin reuptake inhibitor Sertraline versus Cognitive Behavioural Therapy for anxiety symptoms in people with Generalised Anxiety Disorder (GAD) who have failed to respond to low intensity psychological interventions as defined by the NICE GAD guidelines**

### Summary

EudraCT number	2014-004077-16
Trial protocol	GB
Global end of trial date	08 February 2016

### Results information

Result version number	v1 (current)
This version publication date	13 October 2019
First version publication date	13 October 2019

### Trial information

#### Trial identification

Sponsor protocol code	14/0249
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#### Additional study identifiers

ISRCTN number	ISRCTN14845583
ClinicalTrials.gov id (NCT number)	NCT02347033
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	149, Tottenham court Road, London, United Kingdom, W1T 7DN
Public contact	Dr Marta Buszewicz, UCL, +0044 02077940500 x. 31016, m.buszewicz@ucl.ac.uk
Scientific contact	Dr Marta Buszewicz, UCL, +0044 02077940500 x.31016, m.buszewicz@ucl.ac.uk

Notes:

### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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## Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	08 February 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	08 February 2016
Was the trial ended prematurely?	Yes

Notes:

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## General information about the trial

Main objective of the trial:

To assess the clinical effectiveness at 12 months of treatment with the SSRI Sertraline compared to Cognitive Behavioural Therapy (CBT) for patients with persistent Generalised Anxiety Disorder (GAD) which has not improved with low intensity psychological interventions.

NICE guidelines in 2011 established the suggested management of GAD. If symptoms persist after Step 1 conducted in primary care referral to a step 2 low-intensity psychological intervention is recommended. However a significant number of people will not respond to these interventions and require 'stepping up' to a more intensive Step 3 intervention (pharmacological or high intensity psychological therapy).

There is evidence of the clinical and cost-effectiveness of sertraline for GAD compared with placebo and also high intensity CBT compared with wait-list controls, but these findings are not directly comparable and there has been no head to head comparison of the two interventions which was the aim of this trial.

Protection of trial subjects:

Both interventions tested in this trial - the SSRI sertraline and Cognitive Behavioural Therapy (CBT) - are currently available within the NHS for treatment of Generalised Anxiety Disorder (GAD).

Sertraline is licensed for treatment of depression, obsessive compulsive disorder, panic disorder, PTSD and social anxiety disorder with a well-established efficacy profile. The NICE Guidelines Advisory Group proposed it as a first choice pharmacological treatment in GAD although it does not currently have marketing authorisation for this condition. However, in terms of risk of adverse effects, sertraline was the best tolerated medication and the most cost-effective choice.

Potential participants were informed before the baseline assessment that sertraline does not currently have marketing authorisation for GAD, but was recommended in the NICE guidelines and has a well-established safety profile. Prior to assessment their GP was contacted with their consent to ensure there were no medical contra-indications to their being prescribed sertraline if randomised to this intervention arm. At baseline assessment all other inclusion/exclusion criteria were checked, including a negative pregnancy test in females of child bearing potential. The Chief Investigator or other medically qualified persons within the research team reviewed all the eligibility information and if eligibility was confirmed patients were randomised to receive either sertraline or CBT.

After allocation to their intervention groups all trial participants were given contact details for the research team to inform them of any Serious Adverse Events (SAEs) or Suspected Unexpected Serious Adverse Reactions (SUSARs). The patient's GP (sertraline arm) and the IAPT clinical psychologist (CBT arm) were also asked to inform the research team of any such events occurring in trial participants. There was no formal collection of Adverse Events (AEs) as sertraline already has a well-documented safety profile.

Background therapy:

Both intervention groups were free to visit their general practitioner (GP) as they wished to discuss any concerns they might have about their treatment for their generalised anxiety disorder (GAD) or any other medical condition.

In addition patients in the sertraline arm of the trial were encouraged to see their GP for regular prescription and monitoring of this medication - estimated at around 6 visits over a 12 month period according to established clinical guidelines. There were no GP visits specified for patients in the CBT arm of the trial, but they were free to consult as they wished.

As per usual practice the trial participants could be offered other psychotropic medication or

psychotherapy for their GAD as part of their usual care, although we encouraged the GP not to change the patient's medication unless clinically indicated or requested by the patient and not to refer them for CBT whilst in the sertraline arm if possible. We planned to record all use of antidepressants and other forms of counselling or psychotherapy, whether NHS or private, and to take account of these in the analysis.

Usual practice for patients not in the trial would be to allow the patient with GAD to choose, with the help of their GP, between an SSRI and CBT if they fit the criteria for a level 3 intervention and if neither was contra-indicated.

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#### Evidence for comparator:

The comparator in this trial was high intensity Cognitive Behavioural Therapy (CBT).

We used the Dugas and collaborators model for the therapy in this arm. This is one of three CBT protocols for Generalised Anxiety Disorder (GAD) in the UCL CBT Competences Framework ([http://www.ucl.ac.uk/clinical-psychology/CORE/CBT\\_Framework.htm](http://www.ucl.ac.uk/clinical-psychology/CORE/CBT_Framework.htm)) which guides the UK Increasing Access to Psychological Therapies (IAPT) services (<http://www.iapt.nhs.uk/about-iapt/>) to carry out CBT effectively and in line with best practice.

The treatment aims to help affected individuals develop beliefs about uncertainty that are less negative, rigid, and pervasive.

This is accomplished with the use of treatment strategies (such as behavioural exposure to uncertainty, problem-solving training, and imaginal exposure) that aim to help patients confront uncertainty-inducing thoughts and situations. The treatment has been tested in four published randomised clinical trials, with results showing that it is more efficacious than wait-list control, supportive therapy and applied relaxation. The findings also show that 60 to 77% of patients attain GAD remission and that 50 to 55% achieve high end-state functioning following the treatment.

Reference: Dugas, M. J., & Robichaud, M. (2007). Cognitive-behavioral treatment for generalized anxiety disorder: from science to practice. New York: Routledge

Actual start date of recruitment	01 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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### Population of trial subjects

#### Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 5
Worldwide total number of subjects	5
EEA total number of subjects	5

Notes:

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#### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	5
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Due to delays in sponsorship and research governance approvals, recruitment started 5 months later than anticipated.

The study only managed to recruited 5 participants in the first 7 months of the internal pilot as against the target of 40 participants for this period, so after full discussion the study was closed prematurely by the funder.

### Pre-assignment

Screening details:

Potential participants were screened by Patient Well-being Practitioners within local IAPT services at pilot sites.

If after having at least 3 sessions of a low intensity psychological intervention they scored 10 or above on the GAD-7 questionnaire and were thought likely to have GAD the possibility of being assessed for the trial was suggested

### Period 1

Period 1 title	Baseline and trial period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

5 participants were recruited to the study. No final analysis was done as the trial was terminated early due to difficulties in recruitment. Numbers in each arm is estimated from the randomisation scheme.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Study Drug

Arm description:

Sertraline

Arm type	Experimental
Investigational medicinal product name	Sertraline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

25mg increased to 50-100mg/day

<b>Arm title</b>	Cognitive Behavioural Therapy
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Arm description:

Cognitive Behavioural Therapy

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 1</b>	Study Drug	Cognitive Behavioural Therapy
Started	3	2
Completed	3	2

## Baseline characteristics

## End points

### End points reporting groups

Reporting group title	Study Drug
Reporting group description: Sertraline	
Reporting group title	Cognitive Behavioural Therapy
Reporting group description: Cognitive Behavioural Therapy	

### Primary: Final Endpoint

End point title	Final Endpoint <sup>[1]</sup>
End point description:	
End point type	Primary
End point timeframe: Only 5 participants were recruited to the study, no analysis was carried out. Trial was terminated early due to problems with recruitment.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only 5 participants were recruited to the study, no analysis was carried out. Trial was terminated early due to problems with recruitment.

End point values	Study Drug	Cognitive Behavioural Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[2]</sup>	0 <sup>[3]</sup>		
Units: 0				
number (not applicable)				

Notes:

[2] - Only 5 participants were recruited to the study, no analysis was carried out. Trial was terminated e

[3] - Only 5 participants were recruited to the study, no analysis was carried out. Trial was terminated e

### Statistical analyses

No statistical analyses for this end point

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

No adverse events were reported during the brief time period of the trial.

Assessment type	Non-systematic
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### Dictionary used

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Dictionary name	MedDRA
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Dictionary version	18.1
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Frequency threshold for reporting non-serious adverse events: 0 %

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Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No SAEs were recorded during the trial.



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2015	<p>This substantial amendment was done on the recommendation from the Trial Management Group to change the primary outcome measure from the GAD-7 to the 7-Item Anxiety component of the Hospital Anxiety and Depression Scale (HADS-A).</p> <p>This was because the GAD-7 was likely to be routinely collected in the CBT (psychological) arm of the trial but not the pharmacological arm which could prejudice the results.</p>
16 April 2015	Four new pilot sites were added to the study.
23 July 2015	Change in the Principal Investigator at a participating site.
21 September 2015	The Chief Investigator for the study had to step down for 6 months for personal reasons and this position was covered by a co-applicant with considerable experience in running randomised controlled trials in primary care.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
08 February 2016	<p>The trial was prematurely terminated by the funder on the 8th February 2016 because of significant recruitment difficulties which were unlikely to be resolved.</p> <p>At this stage, the trial had recruited only 5 participants. Baseline data was obtained for these 5 participants and 3 month follow-up data from one of these. As the amount of data collected was minimal no analysis was carried out</p>	-

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

As above - because of the premature termination of this trial no results can be reported.

Notes: