VALUeD Final Report

Vascular Augmentation of Late-life Unremitted Depression (VALUeD Study)

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Disclosure of competing interests
None of the authors has any conflicts of interest with respect to the study

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Abbreviations

BDI	Beck depression inventory
BP	Blood Pressure
CARU	Clinical Ageing Research Unit
CAS	Clinical anxiety scale
CCB	Calcium Channel Blocker
CCG	Clinical Commissioning Groups
CLRN	Clinical Local Research Network
CSP	Coordinated System for gaining NHS Permission
EQ VAS	EuroQol visual analogue scale
GCP	Good Clinical Practice
GDS	Geriatric Depression Scale
GP	General Practitioner
HAM-D	Hamilton Depression Rating Scale
MADRS	Montgomery–Åsberg Depression Rating Scale
MHRA	Medicines & Healthcare products Regulatory Agency
MI	Myocardial Infarction
MMSE	Mini Mental State Evaluation
MRI	Magnetic Resonance Imaging
NCTU	Newcastle Clinical Trials Unit
NECS	North of England Commissioning Support Unit
NTW	Northumberland Tyne and Wear
OD	Once daily
PCN	Primary Care Network
PIC	Participant Identification Centre
PIS	Participant Information Sheet
PPI	Public and Patient Involvement
QoF	Quality and outcomes Framework
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RfPB	The Research for Patient Benefit programme
SCID	Structured Clinical Interview for DSM Disorders
STAI	State trait anxiety inventory
TSC	Trial Steering Committee
VRFs	vascular risk factors

1. Trial Information

Study Type:	Double-blind randomised controlled trial (non-commercial pilot study)
CI:	Alan Thomas
Sponsor:	Gateshead Health NHS Trust
Funder:	NIHR RfPB (The Research for Patient Benefit (RfPB) programme)
Site(s):	Single centre; Clinical Ageing Research Unit
Study Medication:	Amlodipine (calcium channel blocker used to treat hypertension and angina)
Question in study:	Does adding Amlodipine help when added to standard antidepressants for patients with unremitting vascular depression?
Trial Registration:	Clinicaltrials.gov Ref: NCT01557153 ISRCTN Ref: ISRCTN46911260 UKCRN Portfolio: 10869
Treatment Period:	16 weeks
Reviews/Follow-up:	final review at 20 weeks
Number of visits:	6, with a 7th for those who achieve remission at week 17.
Data collection:	e-CRF
Questionnaires:	EQ-5D, MADRS, BDI, CAS, STAI, EQ VAS, HAM-D, GDS

Treatment: standard antidepressant + Amlodipine/Placebo

2. Background

Depression has a high prevalence in all ages and about two-thirds of people don't achieve remission with standard antidepressants. In later-life such failure to remit is strongly associated with vascular disease and people with such disease contributing to the development of their depression are said to have 'vascular depression'. Previous evidence has suggested that augmentation of antidepressant treatment with a class of anti-hypertensive drugs, the calcium channel blockers, can improve remission rates in vascular depression. This was a pilot and feasibility study to assess whether a large scale randomised controlled trial of augmentation treatment with the calcium channel blocker amlodipine would be feasible and acceptable in vascular depression.

3. Outcomes:

3.1 Primary

The primary outcome measure is remission (HAM-D<10 for 2 consecutive weeks) by 16 weeks of augmentation.

3.2 Secondary (at 16 weeks):

a. Measure remission (HAM-D<10 for 2 consecutive assessments) by 16 weeks of augmentation.
b. HAM-D reduction in symptoms
c. GDS
d. EQ-5D
e. CGI severity and improvement
f. Instrumental Activities of Daily Living
g. Reduction in symptoms (HAM-D) in those with significant baseline WMH
h. MMSE
i. Blood Pressure
j. Evaluation of effect on perfusion as determined by second MRI scan.

3.3 Primary Objective:

To demonstrate the ability to identify and recruit sufficient numbers of older people with depression from the primary care setting. This pilot study investigates the effects of amlodipine on mood in older people with depression with data collection designed to determine the size and number of centres required for a definitive study to determine efficacy of amlodipine.

The hypothesis is amlodipine augmentation will lead to significantly more people achieving remission at 16 weeks than placebo augmentation. A future definative study would be powered to evaluate this.

4. Methods

Potential participants were identified by screening computerised records in primary care, and secondary care. Local primary care practices were identified in Newcastle and Gateshead through the PCRN and NTW CLRN. Staff at these practices conducted computerised screening and sent out letters to potential study subjects using support from the PCRN/CLRN. Subjects were identified by searching Quality Outcome Framework long term illness databases for people over 50 who were on antidepressant medication, which shows that patients have been assessed as having a depressive illness which needs more than watchful waiting or counselling. Subjects were excluded if they were recorded as: having dementia; on a practice palliative care register and defined as <12 months to live; had a stroke; had a significant psychotic mental illness (bipolar disorder or schizophrenia). The database was also searched for vascular risk factors (VRFs), to identify those with hypertension or those who have two other VRFs as described above and not taking a CCB. Potential participants were also identified from the secondary care network, from relevant clinics within the Gateshead Health NHS Foundation Trust, Northumbria Healthcare NHS Foundation Trust, Northumberland, Tyne and Wear NHS Foundation Trust and Tees, Esk and Wear Valleys NHS Foundation.

5. Visits and assessments.

Assessments were carried out at the Clinical Ageing Research Unit (CARU) at the Campus of Ageing and Vitality at Newcastle University and were additional to any routine clinical visits. Subjects were enrolled in the study for 20 weeks. Those who achieved remission at the final outcome visit (week 16) received an additional assessment at 17 weeks to assess whether remission has been sustained. 7 subjects had a final 20 week assessment.

6. Visit Schedule:

Visits and assessments are outlined in Table 1 and summarised below.

Table 1 – Schedule of assessments

Visit/ Activity	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
	Baseline Assessment, diagnosis & screening	Baseline & Randomisation							Only if patient found to be in remission on	Final Visit
Time	-14 days	0	Week 2 +/- 7 days	Week 4 +/- 7 days	Week 6 +/- 7 days	Week 8 +/- 7 days	Week 12 +/- 7 days	Week 16 +/- 7 days	Week 17 +/- 7 days	Week 20 +/- 7 days
Study discussed	X		Telephone Review & record AEs		Telephone Review & record AEs		Telephone Review & record AEs			
Informed consent	X									
Diagnostic Screen	X							X		
MRI[●1+2]		X						X		
Diagnostic Assessment (SCID)		X								
VRFs recorded	X									
MMSE	X							X		
HAM-D	X	X		X		X		X	X	X
Suicide risk	X	X		X		X		X	X	X
Standing & lying BP[▶]	X	X		X		X		X	X	X
Physical examination		X								
ECG	X									

Haematology & Biochemistry*	X							X✞		
CIR-G		X						X	X	
GDS		X						X	X	
EQ-5D		X						X	X	
CGI		X						X	X	
IADL		X						X	X	
Randomisation (after all eligibility checked)		X								
Study medication dispensed		X		X		X				
Study medication checked				X		X		X		
Adverse events				X		X		X		
Concomitant medications		X		X		X		X		

Week	Visit title
-2 days	Visit 1 – screening, diagnosis and consent
0	Visit 2 – Baseline assessment and randomisation
2 (+/- 7 days)	Visit 3 – follow up 1
4 (+/- 7 days)	Visit 4 – follow up 2
8 (+/- 7 days)	Visit 5 – follow up 3
16 (+/- 7 days)	Visit 6 – final outcome
17 (+/- 7 days)	Visit 9 – final remission visit

7. Important changes to methods

Aims and Objectives

List of substantial amendments submitted to MHRA that made significant changes to the way that the study was conducted.

Amendment	Date of submission	Detail	Approved Date
8	06/03/2013	Extra exclusion criteria	08/04/2013
10	04/07/2013	Exit strategy removal	29/07/2013

Amendment 10 was a change to the exit strategy. Following a meeting of the DMEC, the committee agreed that unblinding the patients prior to study completion and data analysis may cause bias within the study due to associated unblinding of study staff. Unfortunately an internal error within CSP caused a delay in this amendment being approved by the Newcastle upon Tyne Hospitals NHS Foundation Trust. By the time that the approval came through, all patients had completed the trial and therefore consented to the earlier version of the PIS. 5 of the 8 participants requested to be unblinded in total.

8. Research Plan and Methodology

Amendment	Date of submission	Detail	Approved Date
2	02/02/2012	Add Gateshead Trust as PIC, update search criteria for PICs	08/03/2012
3	28/03/2012	Update visit window for MRI scans in protocol	24/05/2012
4	18/06/2012	Update study medication label to include a pack number	04/07/2012
6	28/08/2012	Amendment to recruitment strategy, addition of secondary care PICs/sites	02/10/2012
7	13/11/2012	Update MMSE and blood pressure reading details in protocol	18/12/2012

Amendment 6 was decided following a Trial Steering Committee meeting. The members agreed that recruitment via primary care was relatively low and very slow to recruit. At the time of the amendment, the response rate was only 3.7%. It was felt that a change in the recruitment strategy was necessary.

9. Participants

Eligibility criteria

- Age $\geq$ 50 years
- Clinically significant (unremitted) vascular depression, as defined above.
- MMSE >23
- Medically stable
- BP < 150/90 (QoF Audit standard)
- Patient has provided written informed consent for participation in the study prior to any study specific procedures

Exclusion criteria

- Taking a calcium channel blocker
- BP < 110/70
- Orthostatic hypotension
- Clinical evidence of dementia
- History or clinical evidence of stroke
- History of bipolar or psychotic disorder
- Significant suicide risk
- Known hypersensitivity to amlodipine or any other calcium channel blocker
- Severe renal or hepatic impairment
- Aortic Stenosis

- Pregnancy, or women planning to become pregnant within next 12 months, or women who are breast feeding.
- Use of other investigational study drugs within 30 days prior to study entry (defined as date of randomisation into study)
- Previous participation in this study
- Presence of cardiac pace-maker or other contraindications to (only applies to those consenting to MRI sub-study)

Settings and locations.
Assessments were carried out at the Clinical Ageing Research Unit (CARU) at the Campus of Ageing and Vitality at Newcastle University.

10. Consent of Participants
All potentially eligible subjects identified by screening received a letter from their primary or secondary care practitioner inviting them to participate and giving contact details for Dr Thomas and the research team based at the Clinical Ageing Research Unit (CARU) on the Campus for Ageing and Vitality in Newcastle. Those who responded were given the opportunity to discuss the study over the telephone and offered the chance to visit the research site to discuss the study in detail. They were also sent a copy of the main study information sheet by the research team based at the study site for further consideration.

Those willing to participate gave written informed consent by signing and dating the study consent form, which were witnessed and dated by Dr Thomas, who has training and experience in taking consent in RCTs and up to date GCP training (Good Clinical Practice for Principal Investigators: Newcastle Clinical Research Centre, March 10th 2009). In his absence consent was taken by similarly trained and experienced staff (as per delegation log) involved in the study, including medical staff and research nurses, with opportunity for participants to ask any questions. All study subjects had mental capacity to give such consent. Dr Thomas and the other staff at CARU are experienced in assessing mental capacity and familiar with the Mental Capacity Act. The exclusion criteria made it unlikely that someone lacking capacity to consent would have been identified as a potential study participant, and this did not happen during the study. Written informed consent was obtained prior to randomisation and prior to study specific procedures or investigations.

The original signed consent forms and copies of the corresponding Patient Information Leaflets were retained in the Investigator Site File, with a copy in the clinical notes and a copy provided to the participant. The participant specifically consented to their GP being informed of their participation in the study.

Due to the small subject population, the information sheets and consent forms for the study were only available in English. There was no requirement for the use of interpreters, either for verbal translation or for deaf subjects, during the study.

A screening log was maintained to document details of subjects invited to participate in the study. For subjects who declined participation, this was used to document any reasons for non-participation where possible. The log also ensured potential participants were only approached once.

Following consent, the full baseline assessment, including a SCID assessment (Structured Clinical Interview for DSM Disorders (a diagnostic instrument for depression)) was completed. Subjects were then randomised and given their blinded study medication.

11. Patient and Public Involvement (PPI)

This study was developed in consultation with Voice North and Years Ahead: North East Regional Forum. They were involved with the design and management of the research. Voice North was also involved in undertaking the qualitative component of the study. Voice North reviewed the patient information sheets and consent forms for the study.

Two patient representatives were identified to participate in the Trial Steering Committee. The feedback provided by the lay members during the early stages of study set-up resulted in a significant amendment to the study in order to remove the need to send potential participants the extensive Patient Information Sheet by the addition of a summarised Patient Invite Letter.

12. Results

The areas covered by this study for recruitment were (in their current CCG format); Newcastle North and East; North Tyneside; Northumberland; Newcastle West; Sunderland; Gateshead; South Tyneside. This catchment area has a total of 281 general practices.

Practices

We were informed by NECS (commissioners) that 72 practices were approached about the study. However we were not provided with sufficient information regarding how practices had been approached, or the reasons why they declined to participate, and we are therefore unclear what 'being approached' meant. It appeared to the research team that practices who were approached with full study information participated. Of the 72 practices apparently informed about the study, 51 ‘did not respond’, 5 declined participation (without explanation), and 16 carried out the electronic search of patient records. It also appears that practices experienced some problems in executing the electronic search strategy that we had agreed with commissioners and therefore on some occasions (number unknown) the wrong patient search criteria may have been used.

13. Patients:

13.1 Primary care

236 invitations were sent to patients (an average of 15 in each of the 16 practices)
Of these 10 responded and were screened in our Clinical Ageing Research Unit
Rate = 10/236 = 4.2% (95%) CI: 2.1 to 7.7%)
All 10 patients were consented.
Of the 10 consented patients, 8 were recruited into the study.
Rate = 8/10 = 80% (95% CI: 44.4 to 97.5%)

Attempts to Improve Recruitment

During the course of the study, we asked if the research team could approach general practices directly to invite them to participate, but were told that we were not allowed to, and that all contact must be made via PCT/NECS (commissioning services). Previous experience from one of the co-applicants showed that approaching practices directly for another study, led to a significantly higher number of participants being recruited. Practices were a lot more engaged with that study and received direct support from the study team.

Following an amendment suggested by the TSC, screening also took place in secondary care within 5 NHS trusts in the North East (the Newcastle upon Tyne Hospitals NHS Foundation Trust; Tees, Esk and Wear Valley NHS Foundation Trust; Northumbria Healthcare NHS Foundation Trust; Northumberland, Tyne and Wear NHS Foundation Trust; and Gateshead Health NHS Foundation Trust).

13.2 Secondary care:

15 patients were screened. We were unable to obtain actual numbers of invitations sent from secondary care. 0 were recruited into the study.
Rate = 0/15 = 0.0% (95% CI upper bound 18.1%)
In total, therefore, of the 251 patients invited from primary care and screened from secondary care, 8 were recruited into the study.
Rate = 8/251 = 3.2% (95% CI: 1.4 to 6.2%)

13.3 Feasibility Conclusions

The study was successful in demonstrating that it was not feasible to recruit to a study with this design under current circumstances. We found we could not identify sufficient patients from primary or secondary care.

The percentage of practices who participated is small (less than 25%) in comparison to the number throughout the region, which contributed to the small number of participants recruited. With a practice participation rate of 22%, an average of 15 patients identified per practice, and a recruitment rate of 3% of those patients identified, then if all 281 practices in

the region had been approached using the systems in place during this study we would have recruited about 45 patients.
To achieve our target of 80 participants, using this rate of conversion, 2400 invitations would need to have been sent out; this would have required the participation of 160 practices at the rate of observed patient identification per practice.

Unfortunately, however, we don't have the quality of information to draw these conclusions with confidence. This is an important issue because we remain unclear about whether the target group of patients ('vascular depression') exists in sufficient numbers in primary care, as previous research suggests, and our failure to recruit to target is due to problems with current systems of practice recruitment, patient identification and recruitment. An alternative explanation is that the target group is not large enough to support such a study even if all potential subjects could be identified. Perhaps the use of the Clinical Practice Research Datalink would have enabled us to clarify this important question.

14. Study Acceptability

8 patients were randomised into the study, 7 completed the study (as defined by compliance with the 16 week follow-up visit (visit 8) for the primary outcome). 1 additional patient attended the screening visit but was not randomised. 6 patients attended the final visit 10 at 20 weeks.
Rate of completion = 7/8 = 87.5% (95% CI: 47.3 to 99.7%)
(Rate for 20 week visit = 6/8 = 75.0% (95% CI: 34.9 to 96.8%))

14.1 Study compliance rate:

Compliance was assessed at Visits 4, 6, 8 (weeks 4, 8, 16). Full compliance was defined as compliance at every visit. If a single visit showed non-compliance, full compliance was determined as not possible. Where any available data showed compliance at some visits but there were missing data for other visits, full compliance for that patient was declared as 'missing'.

Data on full compliance was available for 4 patients of the 8 randomised patients; 3 completed the study with full compliance to their allocated intervention.
Rate = 3/4 = 75.0% (95% CI: 19.4 to 99.4%)

14.2 Acceptability Conclusions

In summary, therefore, for those patients who consented, there were very good completion and compliance rates, which is in line with our predictions. The study design appeared acceptable to patients.

15. Analysis

Analysis was by intention to treat following random allocation to study arm in a 1:1 ratio. Randomisation was performed via a web based system using random permuted blocks and was stratified by severity (defined by a dichotomous variable indicating whether baseline HAM-D was less than or greater than/equal to 15). The study was double-blind. Participants were allocated to one of the following groups:

- Amlodipine plus standard antidepressant treatment
- Placebo plus standard antidepressant treatment

Of the 8 recruited and randomised:

- Amlodipine: n=4
- Placebo: n=4

As a result of this small achieved sample size the analysis plan was altered from that described in the protocol. There was no comparative hypothesis testing and instead summary statistics were calculated for pre-specified outcome variables by arm.

15.1 Amlodipine group:

4 patients were recruited into this group, 2 achieved remission at some point in the study period up to week 16. Complete HAM-D data was not available for 1 patient for whom it was deemed that remission at any point was not possible as data from all previous visits was available and showed HAM-D≥10.

Rate = 2/4 = 50.0% (95% CI: 6.8 to 93.2%)

By week 17 (visit 9 – this only took place if a patient was actually in remission at week 16) remission at any point during the study could be determined for 3 patients; 2 achieved remission at some point.

Rate = 2/3 = 66.7% (95% CI: 9.4 to 99.2%)

By week 20 remissions at any point during the study could be determined for 2 patients; both achieved remission at some point.

Rate = 2/2 = 100.0% (95% CI lower bound: 22.4%)

15.2 Placebo group:

4 patients were recruited into this group, 3 failed to achieve remission at any point in the study period up to week 16. Complete HAM-D data was not available for 1 patient for whom it was not possible to determine whether remission was possible.

Rate = 0/3 = 0.0% (95% CI upper bound: 63.2%)

By week 17 remission status could be determined for 3 patients; none achieved remission at any point in the study.

Rate = 0/3 = 0.0% (95% CI upper bound: 63.2%)
By week 20 remission status could be determined for 2 patients; none achieved remission at any point in the study.
Rate = 0/2 = 0.0% (95% CI upper bound: 77.6%)

15.3 Interpretation

This analysis is descriptive only. As a result of the achieved sample size no statistical comparison has been made between the trial arms.

16. Lay Summary

Depression has a high prevalence and two-thirds will not improve with routine treatment. About half have a form of depression known as vascular depression. In this study we augmented antidepressant treatment with a vascular treatment (a BP drug called amlodipine) to determine if this is effective in vascular depression. We aimed to find out if giving amlodipine to people with non-responding vascular depression would be acceptable and whether it would be feasible to recruit such patients through their GPs. We also wanted to know whether "augmentation" might have a measureable benefit for patients. Ultimately, we wanted to use the findings from this study to inform the design of a larger study, if this one showed was shown to be feasible and acceptable, and the treatment appeared promising.

72 of 281 general practices in the North East were informed of the study but we do not know whether they were simply notified at GP forums, or approached individually and offered support. Nor could we confirm if 72 was the total for the region. In the South of Tyne area, we learned that of 31 research active sites only 5 were approached. For those practices agreeing to participate it appears that the electronic search strategies used for patient identification were not those we had defined, because practices found it difficult to use the search strategy we had agreed with GP commissioners. This pilot study therefore encountered considerable difficulties in recruitment at both site (general practice) and patient level. Positively, amongst those patients identified and who consented to participate there were very good completion and compliance rates (about 80%), in line with our predictions. We were unable to clarify whether the reason for non-recruitment was because patients with ‘vascular depression’ do not exist in sufficient numbers or that there are sufficient patients with vascular depression but that the systems we had to work with were unable to identify them. In the latter case a different system for patient identification, such as the Clinical Practice Research Datalink (CPRD), might have been successful

16.1 Conclusions

- The study successfully showed that it was not feasible to recruit to such a study of vascular depression from primary or secondary care under current circumstances.

- We found that the design of the trial was acceptable to patients as we had good completion and compliance rates
- The low numbers precluded comparative hypothesis testing

17. Intervention

Study medication was labelled according to the requirements of Volume 4 European Union Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Annex 13. All study medication was dispensed from the Pharmacy in Northern Centre for Cancer Care at the Freeman Hospital. Encapsulation of amlodipine and placebo was carried out by Newcastle Specials Pharmacy Production Unit. This study medication was for use by trial participants only and was paid for by this study.
Active and placebo study medication was provided as a 4 week initial supply of 5mg capsules followed by total of 12 week's supply of 10mg, dispensed at week 4 and week 8.

Week 1: 1 bottle/container (35 x 5mg once daily (od))
Week 5: 2 bottles/containers (35 x 5mg od) to provide 10mg dose od
Week 9: 4 bottles/containers (35 x 5mg od) to provide 10mg dose od

Subjects were commenced on 5mg/day amlodipine (or matched placebo) for four weeks. If there were no adverse effects at 5mg/day related to amlodipine the dose was increased to 10mg/day at four weeks. If adverse effects were present which were tolerated, the dose was maintained at 5mg/day. If adverse effects developed at 10mg/day, the dose was reduced back to 5mg/day. In the event that intolerable adverse effects developed at 5mg/day, the treatment was discontinued. Where applicable, participants continued on the maximum tolerated dose for 12 weeks (for a total of 16 weeks of medication or identically appearing placebo).

Reassessments occurred in CARU at 4, 8 and 16 weeks after baseline with a final review at week 20. Review included a check of health status (any illnesses, changes in depression), monitoring of adverse events and a pill count to check compliance. At each review we recorded falls and any other reported adverse events, including stroke, Myocardial Infarction (MI) and other vascular events, and assessed lying and standing BP. Each review took approximately 30 minutes. Any participant who reported significant side effects had their dose decreased to 5mg or the medication stopped as clinically indicated. In addition, research staff from CARU telephoned study subjects at weeks 2, 6 and 12 weeks after baseline to enquire about any adverse effects and to provide support.

A seven day visit window was allowed for each 4 weekly dispensing visit. For example, one bottle/container (35 capsules) was dispensed at T_0 for a maximum of 35 days, two bottles/containers (70 capsules) dispensed at T_4 for a maximum of 35 days, four

bottles/containers (140 capsules) dispensed at T8 for a maximum 63 days. Each visit date was planned from the date of T_0, and not the previous visit.

Study medication was prescribed by a study clinician according to the protocol, and dispensed to the patient or clinical staff according to local pharmacy policy. Patients in possession of their study medication were asked to return all trial supplies in their original packaging (even if empty) to the Pharmacist every 4 weeks, starting at T_4. All returned, or unused, study medication was stored in Pharmacy until the end of the study, or until the Trial Manager completed appropriate reconciliation.

Documentation of prescribing, dispensing and return of study medication was maintained for study records.

18. Sample size

80 participants aged over 50 years with unremitted vascular depression.

19. Randomisation and blinding

Randomisation was conducted by the Newcastle Clinical Trials Unit (NCTU) web-based system in a 1:1 ratio stratified by severity (defined by a dichotomous variable indicating whether baseline HAM-D was less than or greater than or equal to 15) and the treatment allocation was kept blind from the subjects and the study assessors and investigators until study completion.

Assignment to either active or placebo arm was blinded to both the participant and investigators/ assessor (double-blind). A set of sealed code-break envelopes were kept in pharmacy; these envelopes were only to be opened in an emergency (preferably with authorisation from the Chief Investigator or Medical Monitor) and the Chief Investigator immediately informed. If the code was broken, details including the participant number, staff member who broke the code, why and when the break occurred would have been recorded and maintained in the site file.

Code breaks were not routinely opened for participants who complete study treatment, but where clinical improvement occurred and the participant wished to have the option of continuing augmentation treatment then unblinding was carried out by pharmacy and the participant and his/her GP informed. Study clinicians and research staff were informed of the result of the unblinding. Following such a code break, the participant and his/her GP consulted about continuing on augmentation treatment. Amlodipine would then be supplied from normal pharmacy stock.

A substantial amendment to not unblind participants who completed study treatment was submitted and approved by MHRA and the Research Ethics Committee (REC), however before it had been approved locally by NUTH, the last participant had requested to be

unblinded, and this request was honoured. In total, 5 participants were unblinded to their treatment following their participation in the trial.

The trial ended as planned at the end of the study as agreed with the funder.

20. Baseline Data

Baseline data of demographic and clinical characteristics are shown in Table 2. The placebo and the amlodipine groups were well balanced on key demographic variables and clinical characteristics.

Table 2: Cumulative Summary Tabulations of Demographic Data

Age range	No of female subjects	No of male subjects	Total No of subjects
50-60	4	3	7
61-70	1	0	1
71-80	0	0	0

21. Response and remission rates

Remission is defined as a Hamilton Rating Scale for Depression score (HAM-D) <10 for 2 consecutive assessments by 16 weeks.

If HAM-D data was missing for a patient at a visit it could not be ascertained positively that remission had occurred. In the event that the previous visit showed a HAM-D≥10 then it was determined that remission had not occurred. If data at a previous visit was missing but data at the current visit available then similarly, remission was declared not to have occurred if the previous visit showed HAM-D≥10. Should these not be the case then remission at that particular visit was declared as missing.

Amlodipine group:

4 patients were recruited into this group, 2 achieved remission at some point in the study period by week 16. Complete HAM-D data was not available for 1 patient for whom it was determined that remission at any point was not possible as data from all previous visits was available and showed HAM-D≥10.

Rate = 2/4 = 50.0% (95% CI: 6.8 to 93.2%)

By week 17, (visit 9 – this only took place if a patient was actually in remission at week 16) remission at any point during the study could be determined for 3 patients; 2 achieved remission at some point.

Rate = 2/3 = 66.7% (95% CI: 9.4 to 99.2%)

By week 20, remission at any point during the study could be determined for 2 patients; both achieved remission at some point.
Rate = 2/2 = 100.0% (95% CI lower bound: 22.4%)

Placebo group:
4 patients were recruited into this group, 3 failed to achieve remission at some point in the study period by week 16. Complete HAM-D data was not available for 1 patient for whom it was not possible to determine whether remission was possible.
Rate = 0/3 = 0.0% (95% CI upper bound: 63.2%)

By week 17 remission status could be determined for 3 patients; none achieved remission at any point in the study.
Rate = 0/3 = 0.0% (95% CI upper bound: 63.2%)
By week 20 remission status could be determined for 2 patients; none achieved remission at any point in the study.
Rate = 0/2 = 0.0% (95% CI upper bound: 77.6%)

Reduction in symptoms:
As measured by the (paired) reduction in HAM-D score (baseline value – week 16 value):

	Amlodipine (n=3)	**Placebo (n=4)**
Mean	5.33	0.25
SD	2.52	3.59
95% CI for mean	-0.92 – 11.58	-5.47 – 5.97
Median	5.00	1.50
IQR	3.00 – 8.00	3.00 – 8.00
Range	3.00 – 8.00	-5.00 – 3.00

22. Harms

Serious adverse events (SAEs)

No serious adverse events were reported during the trial.

23. Generalizability

This study found that it is not feasible to carry out a larger scale study in this patient population using the current primary care systems. The Clinical Practice Research Datalink (CPRD) is an approach that could be used in future studies. This is now considered the gold standard method for clinical trials, and could significantly improve useful data obtained, that has been missing from our study, due to poor communication between the research team and primary care.

Chief Investigator
Dr Alan Thomas

Trial Manager
Mrs Jennie Parker

15 June 2015

Appendices

Appendix 1: Trial protocol
PDF attached separately in additional documentation.

Appendix 2 Statistical analysis plan
PDF attached separately in additional documentation.