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Summary

Title	A multicentre randomised trial to establish the effect(s) of routine administration of Fluoxetine for 6 months in patients with a recent stroke
Short title	**F**luoxetine **O**r **C**ontrol **U**nder **S**upervision
Acronym	FOCUS
Chief Investigators	Professor Gillian Mead & Professor Martin Dennis
Primary Research Question	Does the routine administration of fluoxetine (20mg od) for 6 months after an acute stroke improve patients' functional outcome?
Trial design	An investigator lead, UK based, multicentre, parallel group, double blind placebo controlled trial with broad entry criteria and follow up at 6 and 12 months.
Setting	UK stroke services
Eligibility criteria	**Inclusion** • age ≥ 18 years • brain imaging is compatible with intracerebral haemorrhage or ischaemic stroke • randomisation can be performed between 2 and 15 days after stroke onset • persisting focal neurological deficit is present at the time of randomisation severe enough to warrant 6 months trial treatment from the patient's or carer's perspective **Exclusion** • subarachnoid haemorrhage • unlikely to be available for follow up at 12 months • patient and/or carer unable to understand spoken or written English • other life threatening illness • pregnant or breast-feeding or of child bearing age not taking contraception • history of epileptic seizures • attempted suicide or self-harm • allergy or contra indication to fluoxetine • taken a monoamine oxidase inhibitor in last 5 weeks • taking metoprolol for heart failure • current or recent depression requiring treatment with SSRI • already participating in a CTIMP
Randomisation	Central, via a web based randomisation system utilising a minimisation algorithm
Descriptions of interventions	Fluoxetine 20mg once daily or matching placebo capsules for 6 months.
Outcome measures	Primary outcome measure: modified Rankin scale. Secondary outcome measures: Survival at 6 & 12 months, Stroke Impact Scale, EQ5D-5L, MHI 5, Vitality subscale of SF36, diagnosis of depression, adherence to medication, adverse events, resource use
Follow up	***Local*** at hospital discharge (for inpatients) or ***Central*** at one month (for outpatients) and at 6 and 12 months via postal, web or telephone questionnaires to patients and GPs
Sample size estimate	90% power to detect an improvement in proportion of patients with an mRS of 0-2 at 6 months from 27% to 32.6%.
Number of participants	At least 3000
Statistical methods	Based on an ordinal analysis of mRS adjusted for baseline variables included in minimisation algorithm
Timetable	Start up phase: 2012-2014 Main phase: 2014-2018

1. INTRODUCTION

1.1 Background

The burden of stroke

About 130,000 people have a stroke each year in the UK and, even with acute treatments, about 50% of survivors will have long-term residual disability. This places a huge burden on health and social services and informal carers. Although there is more that can be done to implement treatments that we know are effective e.g. the more widespread provision of thrombolysis and more rapid access to stroke units, there is still an urgent need to identify new treatments that might reduce neurological impairments, disability and dependency after stroke. One promising intervention that needs to be tested is a widely used antidepressant drug, fluoxetine, a serotonin reuptake inhibitor (SSRIs).

Serotonin reuptake inhibitors in animal models

In animals, selective serotonin reuptake inhibitors (SSRIs) have several potentially beneficial effects on both normal and diseased brains. First, they have a neurotrophic effect. Neurotrophins are involved in embryogenesis and organogenesis, they control neural plasticity in adults, regulate synaptic activity and neurotransmitter synthesis and are essential for the regeneration of nerves (Lang 2003). Adult neurogenesis is generally restricted to the subependymal cells of the ventricular system and the subgranular zone of the dentate gyrus in the hippocampus (Ming 2005). SSRI antidepressants increase neurogenesis and expression of neurotrophic/growth factors in the adult hippocampus (Schmidt 2007) and this is likely to account for the behavioural benefits of antidepressants in animals (Santarelli 2005). Importantly, several studies have shown that migration of new neurones to damaged areas of brain may occur (Wiltrout 2007), and that neurogenesis may also occur *within* areas of damaged brain in patients with ischaemic stroke (Taupin 2006). Secondly, fluoxetine may have a neuroprotective effect associated with its anti-inflammatory effect (e.g. repression of microglia activation) (Lim 2009), enhancement of specific protein expression (hypoxia inducible factor – I alpha, hemeoxygenaste-1 (Shin 2009). Thirdly, SSRIs can indirectly affect the adrenergic system through upregulation of beta1 receptors (Palvimaki 1994).

SSRI and motor function in humans

In healthy humans, fMRI studies have demonstrated that fluoxetine can modulate cerebral motor activity (Loubinoux 1999). In 8 patients with pure motor stroke given fluoxetine, there was hyperactivation in the ipsi-lesional primary motor cortex during a motor task; moreover, fluoxetine significantly improved motor skills of the affected side (Pariente 2001). In a small scale randomised trial of patients with unilateral stroke, the administration of citalopram, another SSRI, was associated with a significant improvement in neurological status as measured by National Institute of Health Stroke Score (NIHSS) and a decrease of motor excitability over the unaffected hemisphere measured by transmagnetic stimulation (Acler 2007). Zittel investigated the effects of a single dose of 40mg citalopram in 8 chronic stroke patients. Dexterity was significantly improved (Zittel 2009). In a trial of 52 hemiplegic patients, randomly allocated three treatments (20 mg/d fluoxetine vs 150 mg/d maprotiline vs placebo) for 3 months on a background of physical therapy, those allocated fluoxetine demonstrated the greatest recovery in disability (Dam 1996).

The Fluoxetine on Motor Rehabilitation After Ischemic Stroke (FLAME) Trial is the largest trial to date to evaluate the effects of SSRIs on motor recovery after stroke (Chollet 2011). This

double blind, placebo controlled, multicentre trial randomised 118 patients with ischaemic stroke and unilateral motor weakness to fluoxetine 20mg daily or placebo for 3 months. At day 90, the improvement in the Fugl Meyer motor score from baseline was significantly greater in the fluoxetine group (57 patients, adjusted mean of +34.0 [95% Confidence interval CI 29.7; 38.4]) than in the placebo group (56 patients, adjusted mean of +24.3 [95%CI 19.9; 28.7]; p=0.003). Also, the frequency of independent patients (modified Rankin scale: 0-2) was significantly higher in the fluoxetine group (26.3% vs 8.9%; p=0.015) although there were not significant differences at other cut-offs. Although promising, this study recruited, on average, just three to four patients per year from each of the participating centres, thus limiting the generalisability. All patients also received physiotherapy; so we do not know whether fluoxetine on its own, or with the limited physiotherapy that is available in UK centres, would also be effective. Importantly, we also do not know whether any benefits of fluxoetine persist beyond the treatment period and whether fluoxetine might improve outcome in stroke patients *without* motor deficits. Nevertheless, these promising, but inconclusive results clearly justify further larger trials in patients with motor deficits.

Might SSRIs be of benefit in recovery of non-motor aspects of stroke?

Several recent small studies have suggested the fluoxetine might have other neurological benefits e.g. increased activation of agonist and antagonist muscles in paretic arms after stroke (Berends 2009), improvements in executive function after stroke (Narushima 2007), improvements in alexithymia (unawareness of emotional reactions which is common in right hemisphere strokes) (Spalletta 2006). We do not know whether these beneficial effects of antidepressants are independent of their antidepressant effect (Talleli 2009).

In people with depression, SSRIs modulate the hyperactivity of the hypothalamic pituitary axis (HPA)(Nikisch 2005). After stroke, activation of the HPA axis occurs resulting in hypercortisolism. Hypercortisolism is associated with the development of delirium after stroke and also predicts worse long-term outcome. Thus, SSRIs might, by attenuating the hypercortisolism that is present after stroke, improve outcome, including cognition.

Systematic review of effects of fluoxetine on post stroke outcomes

A systematic review of randomised trials testing whether a course of treatment with fluoxetine started shortly after stroke onset can improve function and prevent post- stroke depression, identified six RCTs published before December 2009 which together randomised 385 patients (Yi 2010). Meta-analysis demonstrated that fluoxetine helped recovery in neurological function (WMD = -4.72, 95% CI -8.31 to -1.13), improved independence in activities of daily living (WMD = -8.04, 95% CI -13.40 to -2.68) and reduced the incidence of post-stroke depression (OR = 0.25, 95% CI 0.11 to 0.56). We have published the protocol for a Cochrane review of Selective Serotonin Receptor antagonists in stroke (Mead 2011). In April 2012, we submitted the completed review to the Cochrane Stroke Group Editorial board. This review identified 56 trials comparing SSRI with a control intervention (e.g. usual care, placebo) given within the first year after stroke. Fifty-two trials (4059 participants) reported data that we could use in the meta-analyses. Of these 52 trials, 28 used fluoxetine and 31 recruited patients within 3 months of stroke onset. The meta-analyses demonstrated beneficial effects of SSRIs on dependency, disability, neurological deficit, depression and anxiety at the end of treatment. There were benefits even in patients without depression at recruitment. However, there was substantial heterogeneity in estimates of effect sizes, sensitivity analyses suggested that methodological limitations of many of the included trials may have led to overestimation of effect sizes, and there was an excess of gastrointestinal side effects in patients receiving an SSRI (Mead et al. 2012). Furthermore, most trials excluded people with cognitive impairment and aphasia; and only eight trials followed patients up after treatment had been discontinued.

Why choose fluoxetine?

There are many SSRI antidepressant medications available. We have chosen to evaluate fluoxetine because it is one of the most widely studied. Its safety profile is very well established, and the drug is well tolerated, in long-term use, even in older subjects. There is more evidence for its effectiveness in stroke than for alternatives, such as citalopram (Mead et al. 2012). A number of manufacturers produce the drug and the price is low which makes it particularly attractive to health services which are under severe cost pressures. Lastly, of all the SSRIs, it has the longest half life, so that gradual reduction in dose is not required when withdrawing the drug (which is inevitable in a trial) to avoid the possibility of an SSRI withdrawal syndrome (NICE 2009).

Potential concerns in stroke: Please refer to appendix 1 below for the latest version of SmPC or online at
http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1472791964904.pdf

There are potential risks associated with giving fluoxetine to a wide range of stroke patients. Its interaction with antiplatelet and anticoagulant medication might increase bleeding risk, although this is usually minor and limited to bruising. Like other antidepressants, fluoxetine may lower seizure threshold, and therefore could increase the frequency of post stroke seizures. . In our Cochrane review, there was a non-significant excess of seizures in patients allocated SSRIs (Mead et al. 2012). We are therefore excluding patients with a history of epileptic seizures. An adverse effect on glycaemic control in diabetics has been recorded. Hyponatraemia is a recognised adverse effect and may prove to be more common amongst stroke patients who may be taking concomitant ACE inhibitors, diuretics and proton pump inhibitors. However, reassuringly, fluoxetine has been very commonly prescribed for several years to patients with stroke to treat depression and emotionalism without major problems emerging. Subject to assessment by the responsible clinician, some stroke patients with severe renal or hepatic failure may not be able to participate in the trial.

Patients commenced on psychotropic drugs, including fluoxetine, are encouraged to monitor its effects on their psychomotor function before resuming driving. However, stroke patients in the UK are advised not to drive for at least a month after a stroke which should provide ample time in the trial for any potentially important adverse effects which would influence their driving ability to become apparent.

1.2 Rationale for the study

The need for large randomised trials of fluoxetine in stroke

Given these encouraging data, which suggest that fluoxetine might have substantial benefits for a wide range of stroke patients there is an urgent need to carry out randomised trials which have adequate power to reliably detect clinically important benefits. Given that fluoxetine is inexpensive (only about £2.50 per month in UK), simple-to-administer and generally well-tolerated, if it had an effect which was a fraction of that seen in the FLAME trial it would be a very worthwhile treatment for patients, their carers and health and social services.

The need to identify the patients who might particularly benefit from treatment

Whilst fluoxetine may improve outcome for the whole range of stroke patients, it is also plausible given its diverse pharmacological effects that the balance of risk and benefit may vary in patients with different types of stroke. For instance, pre-clinical work has suggested that motor recovery may be specifically enhanced (see above). Also, fluoxetine influences bleeding risk, particularly in those taking antithrombotic medication, so there could be differences in effectiveness between patients with ischaemic (who are taking antithrombotics) and those with haemorrhagic stroke. Patients with severe stroke associated with cognitive and communication problems may be at greater risk of adverse effects because patients are unable to report early problems but they might also have more to gain from a treatment which enhances recovery. Also, patients with severe strokes are normally at greater risk of post stroke depression (which is associated with stroke severity) but – as a consequence of their deficits - are at greater risk that their post stroke depression is not recognised and so goes untreated.

2. STUDY OBJECTIVES

The trial aims to robustly address several research questions.

2.1 Objectives

2.1.1 Primary Objective

Does the routine administration of fluoxetine (20mg od) for 6 months after an acute stroke improve patients' functional outcome?

2.1.2 Secondary Objectives

1. If fluoxetine improves functional outcome, does any improvement persist after treatment is stopped?

2. Does the routine administration off fluoxetine (20mg od) for 6 months after an acute stroke causing motor impairment improve patients' motor function and does any improvement persist after treatment is stopped?

3. Does the routine administration of fluoxetine (20mg od) for 6 months after an acute stroke causing communication impairment improve patients' communication function and does any improvement persist after treatment is stopped?

4. Does the routine administration of fluoxetine (20mg od) for 6 months after an acute stroke causing impairments which precludes the formal assessment of post stroke mood improve patients' functional outcomes?

5. Does the routine administration of fluoxetine (20mg od) for 6 months after an acute stroke improve patients' outcome with respect to mood, fatigue, cognition, health related quality of life or participation and does any improvement persist after treatment is stopped?

6. Does the routine administration of fluoxetine (20mg od) for 6 months after an acute stroke reduce the cost of health and social care over the first year?

7. Does the routine administration of fluoxetine (20mg od) for 6 months after an acute stroke increase the risk of serious adverse events?

2.2 Measure of outcome

2.2.1 Primary measure of outcome

Modified Rankin Scale (mRS) (based on Ordinal analysis to maximise power and to avoid problem of including patients with a mRS >2 prior to their stroke) at 6 months after randomisation. . We will also collect data on mRS at 12 months (one of our secondary objectives). Patients who die would be attributed a score of 6 for this analysis.

The mRS is an extremely simple, time efficient measure with well-studied reliability used to categorize level of functional outcome. It has been used extensively in large, multicentre stroke trials.

Any misclassification of patients into an inappropriate mRS category may reduce the power of the trial. To minimise misclassification and intermodality differences we will use the simple modified Rankin Scale questionnaire (smRSq) described by Bruno and colleagues. This has been delivered by both telephone and postal questionnaires and has been completed by patients and proxies (Bruno 2010, 2011, Dennis(2012)).

2.2.2 Secondary outcome measures

To answer our secondary objectives, we will collect the following outcome measures:

- Deaths from all causes by 6 and 12 months. Death from all causes until the end of the trial ascertained through data linkage.

- The EuroQol (EQ5D-5L) to provide an overall measure of health related quality of life (HRQOL) and to allow a health economic analysis based on quality adjusted life years (Herdman (in press))

- The mental health inventory 5 (MHI 5) will provide a measure of depression and anxiety. This brief measure performs well, compared with longer questionnaires (e.g. MHI-18, GHQ-12, GHQ-30, in the detection of depression and anxiety (Berwick 1991, McCabe 1996, Hoeymans 2004)

- The vitality subscale of the SF36 will be used to assess patients level of fatigue (Mead 2007; 2011)

- The Stroke Impact Scale (SIS) will provide an overall assessment of patient outcome as well as allowing us to assess the effect of treatment on specific outcomes of importance to the patients. The SIS is a stroke-specific, comprehensive, health status measure. The scale was developed with input from both patients and caregivers and includes 8 domains (strength, hand function, ADL/IADL, mobility, communication, emotion, memory and thinking, participation) from across the full impairment-participation continuum (Duncan 1999; 2003). It also provided an overall assessment of recovery. The scale has been evaluated successfully for use by proxy respondents and has been delivered as both telephone and postal questionnaires (Duncan 2002; 2005, Kwon 2006).

- New diagnosis of depression since randomisation. We will record whether it resulted in a referral for specialist assessment, whether the diagnosis was confirmed by a psychiatrist or psychologist and whether antidepressant medication was initiated and whether there was any attempt at suicide or self harm.

- Other adverse events including: further strokes, acute coronary events, upper gastrointestinal haemorrhage, falls resulting in injury, new fractures, epileptic seizures, symptomatic hypoglycaemia (<3 mmol/l), hyperglycaemia (>22mmol/l) hyponatraemia (<125mmmol/l)

- Health and social care resources used during follow up including: days in hospital and days in care home since enrolment; and intensity of formal carers at home – total number of visits per week at the time of follow up.

- Adherence to FOCUS trial medication

3. STUDY DESIGN

The FOCUS trial (**F**luoxetine **O**r **C**ontrol **U**nder **S**upervision) will be an investigator lead, UK based, multicentre, parallel group, double blind placebo controlled trial with broad entry criteria and follow up to ascertain the primary and secondary outcomes at 6 and 12 months.

3.1 Start up phase

A start up phase lasting approximately two years will establish whether our protocol is feasible. It will enable us to establish: a core trial management team, an IT system to manage web based randomisation, drug allocation, stock control, follow up, data collection and verification, and important aspects of feasibility including recruitment, medication adherence, questionnaire response and follow-up rates.

Specifically, the start-up phase will provide estimates of:

1. the range of recruitment rates per hospital and thus the likely number of centres and duration of the main phase. It will also help identify barriers to recruitment which may allow us to increase recruitment rates.
2. the recruitment into our pre-specified subgroups (those with motor and language deficits).
3. what proportion of patients can consent for themselves?
4. the adherence rate, and reasons for non adherence, which will influence our predicted effect size and power calculations. A review of the data accumulated during the feasibility phase will be used to refine and simplify the trial procedures to maximise adherence.
5. the response and completion rates for postal, telephone, web based and face to face questionnaires at each of our planned follow-ups? This is important as it will determine the likely resources needed to optimise completion (with telephone and face to face follow-up) and rates of missing data which will influence our power.
6. The response rates from General Practitioners, to our questionnaires at 1 month (for outpatients), 6 months and 12 months (for patients recruited either as inpatients or outpatients).

The DMC charter specifies the conditions under which the DMC would recommend release of the unblinded trial results to the investigators and the trial steering committee, and the TSC would decide whether to continue recruitment or not.

We do not intend to perform an interim analysis at the end of the feasibility study.

Provided that the start-up phase proceeds as expected and

a) In the view of the DMC after their confidential review of the accumulated safety and efficacy data, there is no clear indication to modify the protocol, AND
b) The Trial Steering Committee are satisfied the feasibility criteria have been met

we would aim to move seamlessly from the start-up phase to the main phase of the trial, without interruption of recruitment and without reference to any analyses of treatment effects based on the available trial data. This model has successfully been used to perform several large multicentre trials in stroke, e.g. IST, IST-3, FOOD, CLOTS 1&2, CLOTS 3.

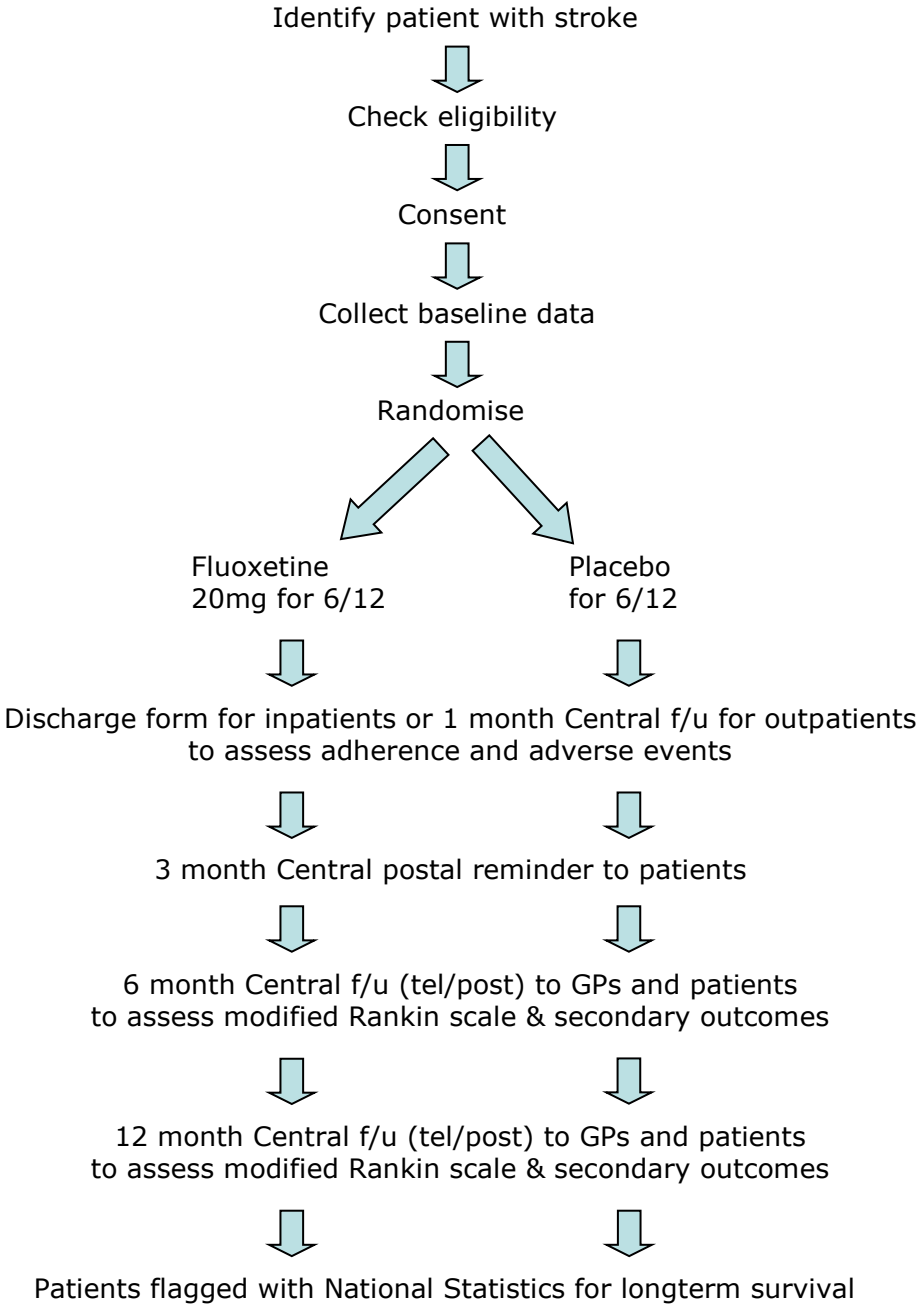
3.2 Main Phase

The main trial will be powered to detect differences in a primary outcome of modified Rankin score for the entire group, and also powered to detect differences in specific outcomes in pre-specified subgroups based on their neurological deficits at baseline and pathological type (haemorrhage vs infarction) .. Because it may not be feasible to enrol sufficient patients to reliably detect moderate effect sizes in these subgroups on our primary outcome (modified Rankin scale) we will introduce two strategies:

1. Collect outcome measures which are likely to be more sensitive than our primary outcome to the possible benefits of fluoxetine in specific subgroups.

2. To work collaboratively with a parallel trial (AFFINITY trial) based in Australia (which shares steering group members with FOCUS) and possibly another in Scandinavia (EFFECTS trial) which both have a very similar design to FOCUS. This will increase the overall sample size and the numbers of patients in each of the important subgroups. We will perform pre-specified meta-analyses to maximise our chances of detecting benefits in specific subgroups.

Flow diagram



4. STUDY POPULATION

4.1 Number of Participants

The start up phase will enrol about 200 patients. The main phase will enrol at least an additional 2800 patients. A total of at least 3000 patients will be enrolled.

4.2 Inclusion criteria

- Age ≥ 18 years
- Brain imaging is compatible with intracerebral haemorrhage or ischaemic stroke
- Randomisation can be performed between 2 and 15 days after stroke onset
- Persisting focal neurological deficit is present at the time of randomisation. This needs to be severe enough to warrant 6 months treatment with the FOCUS trial medication from the patient's or carer's perspective. (N.B. Unless the patient or carer thinks that their residual deficits are severe enough to make 6 months treatment with Fluoxetine potentially worthwhile, they are unlikely to consent, and even if they did they, are unlikely then to adhere to the treatment).

4.3 Exclusion Criteria

- Subarachnoid haemorrhage (except where secondary to a primary intracerebral haemorrhage).
- Unlikely to be available for follow-up for the next 12 months e.g. no fixed home address
- Unable to speak English AND no close family member available to help with follow up forms
- Other life threatening illness (e.g. advanced cancer) that will make 12-month survival unlikely
- History of epileptic seizures
- History of allergy to fluoxetine
- Contraindications to fluoxetine including:
    - hepatic impairment (ALT > 3 upper normal limit)
    - renal impairment (creatinine levels >180 micromol/l)
- Pregnant or breast-feeding, women of child bearing age not taking contraception. Minimum contraception is an oral contraceptive
- Previous drug overdose or attempted suicide
- Already enrolled into a CTIMP
- Current or recent (within the last month) depression requiring treatment with an SSRI antidepressant,
- Current use of medications which have serious interaction with fluoxetine
    - use of a monoamine oxidase inhibitor (MAOI) during the last 5 weeks (e.g. phenelzine, isocarboxacid, tranylcypromine, moclobemide selegiline and rasagiline)
    - pimozide
    - metoprolol for heart failure

Co- administration of fluoxetine and a Mono Amine Oxidase Inhibitors (MAOI) may result in life threatening interactions. Therefore, patients on MAOI inhibitors are ineligible for the FOCUS trial. Also, any patient needing treatment with a MAOI must stop their trial treatment for at least 5 weeks before commencing the MAOI.

4.4 Co-enrolment

Inclusion in another research study, including another randomised controlled trial, does not automatically exclude a patient from participating in FOCUS. As long as inclusion in the other study would not confound the results of FOCUS or make attribution of adverse reactions difficult, co-enrolment is permissible.

However, if a participant has already been enrolled into another CTIMP, they cannot be enrolled into FOCUS. If a patient is enrolled into FOCUS, they may not subsequently be enrolled into another CTIMP. Also, local researchers must avoid overburdening patients.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 Identifying participants

The randomising clinician or nurse should try to identify potentially eligible patients within the first week after stroke onset, either during an inpatient stay or outpatient clinic. The patient, or their personal legal representative (if the patient lacks capacity to consent for themselves), should be approached by a member of the clinical team looking after that patient to ascertain their interest in participating in the trial or to obtain their permission to pass their details onto any research staff involved. Research nurses may approach patients directly if they are part of the clinical team and have a role in patient care. This is important to maintain patient confidentiality.

5.2 Consenting participants

The Investigator is responsible for ensuring informed consent is obtained and the and the consent form completed, signed and dated by all parties prior to any protocol specific procedures being carried out. The decision to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants or legal representatives must receive adequate oral and written information – appropriate Participant Information Booklet (PIB) and Informed Consent Forms (ICF) will be provided. The oral explanation to the participant should be performed by the Investigator or designated person, and must cover all the elements specified in the PIB/ICF(s). The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which he/she otherwise would be entitled.

The participant should be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) and agree that the information held and maintained by The Health and Social Care Information Centre and other central UK NHS bodies can be shared with us and may be used to help contact them or provide information about their health status.
The patient should be given ample time to consider giving their consent for the study. The date that the PIB is given to the patient must be documented within the patient's medical records.

The Investigator or delegated member of the trial team and the participant should sign and date the ICF(s) to confirm that consent has been obtained. The participant should receive a copy of this document, a copy filed in the patient medical records, a copy faxed to the trial co-

ordinating centre and the original filed in the Investigator Site File (ISF). Full details of the consent process should also be recorded in the patient's medical records. A copy of the PIB should be filed in the patient's medical notes. The patient should retain their copy of the PIB, which, along with a copy of the completed consent form, should be included in the Discharge pack when the patient is discharged from the hospital.

Laws governing consent procedures, and in particular those governing incapacitated adults and their involvement in research, must be followed. Written informed consent from the patient should always be sought where possible. If this is not possible because the patient cannot write, the randomising clinician or nurse can gain witnessed verbal consent.

5.2.1 Consenting patients who lack capacity to consent themselves

If a patient lacks capacity to consent for themselves then a personal legal representative may consent on the patient's behalf. We will not accept consent given by a professional legal representative. The table below specifies the hierarchy which should be applied in England, Wales and Northern Ireland and Scotland where the laws differ slightly.

Hierarchy of informed consent for an incapacitated adult	
England, Wales and Northern Ireland	***Scotland***
1. Personal legal representative A person not connected with the conduct of the trial who is: (a) suitable to act as the legal representative by virtue of their relationship with the adult, ***and*** (b) available and willing to do so.	*1. Personal legal representative* 1A. Any guardian or welfare attorney who has power to consent to the adult's participation in research. 1B. If there is no such person, the adult's nearest relative as defined in section 87(1) of the Adults with Incapacity (Scotland) Act 2000.

5.2.1.1 Re-consenting patients who regain capacity

If the patient regains capacity during any hospital stay, the patient should be informed about their enrolment into the study and fully informed consent should be obtained from the patient. If the patient regains mental capacity after hospital discharge but during the follow up we will not attempt to "re consent" at that stage. This is because the nature of the follow up will make it impractical to know whether the patient has regained capacity. Also, the patient who does regain capacity will have the option of not taking the trial medication and not completing the follow up assessments and thus by default remove themselves from the study.

5.2.2 New Safety Information

If any new safety information becomes available which may result in significant changes in the risk/benefit analysis, the PIB and ICF must be reviewed and updated accordingly. All subjects that are actively enrolled on the study will be informed of the updated information and given a revised copy of the PIB/ICF in order to confirm their wish to continue on the study.

5.2.3 Signed consent forms

The patient or personal legal representative should receive a folder including a copy of the relevant version of the PIB, a copy of the completed ICF, and a patient diary which contains contact details for the trial co-ordinating centre and prompts the recording and reporting of adverse event etc. The original ICF and PIB used should be filed in the Site File with the randomisation form.

The completed ICF should be faxed to the trial office, or scanned and uploaded onto the secure trial website prior to randomisation. The trial management system will prompt them to do so via email and/or fax until the consent form has been received.

5.3 Screening for eligibility

Members of the clinical team, including research nurses working should screen admissions to the stroke service to determine if they meet the inclusion criteria. This will give ample time for the patients and/or their families to consider the trial materials, ask questions and still be recruited between 2 and 15 days after stroke onset.

5.4 Ineligible and non recruited patients (Screening logs)

Screening logs are not part of the FOCUS data collection process. Whilst we acknowledge that a screening log may provide information about the generalisability of the trial results, it is likely to represent substantial effort for participating centres, and may divert time from the key tasks of treating and recruiting patients.

6. RANDOMISATION

6.1 Randomisation

Having obtained consent, the randomising person collects the baseline data necessary to complete a randomisation form and enters the patient's baseline data into our computerized central randomisation service by means of a secure 24/7 Web interface or a telephone call to the trial office during office hours. After the computer program has checked these baseline data for completeness and consistency it allocates that patient a unique study identification number and a treatment pack number which corresponds to either Fluoxetine or Placebo. The system applies a minimisation program to achieve balance for four factors:

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- Delay since stroke onset (2-8 vs 9-15 days)
- Predicted 6 month outcome (based on the six simple variable model (Counsell 2002).
- Presence of a motor deficit (based on NIHSS)
- Presence of aphasia (based on NIHSS)

The randomisation form should be filed in the site file. Detailed notes of the consent procedure and patient's participation in the trial must be recorded in the patient medical records for any future source data verification. This should include the date of consent, that the patient received the PIB, who obtained consent and signed and dated confirmation by a physician sub-investigator that the patient was eligible for enrolment. Lack of capacity should also be documented if this is absent.

Following randomisation, the trial co-ordinating centre will generate and send a letter to inform the GP of the patient's enrolment in the trial, including a copy of the consent form, and the follow-up schedule.

6.2 Treatment Allocation

The minimisation algorithm randomly allocates the first patient to a treatment, but allocates each subsequent patient to the treatment that leads to the least difference between the treatment groups with respect to the prognostic factors (Altman 2005). To ensure that we retain a random element to treatment allocation, patients will be allocated to the group which minimizes differences between groups with a probability of 0.8. The system contains a list of treatment codes for each centre and which match the stocks held at that centre. At the end of the session each patient is allocated a treatment code which corresponds to either an active

(f.luoxetine 20mg once daily) or placebo treatment pack which contains six months supply of capsules held at that centre.

The randomisation system will take account of the drug stocks held locally to firstly ensure the allocated treatment is available and second to minimise wastage. The randomisation system will automatically generate an email/fax to the centre coordinator and the local research pharmacist to ensure that the allocated treatment is prescribed. The pharmacist or coordinator may access treatment codes, to replace lost study medication through a secure website by entering the patient's study ID number and date of birth.

To facilitate drug reconciliation and stock control the pharmacist or local coordinator will remove the adhesive treatment number label (flag) from the medication bottle, stick it onto the confirmation of allocation fax and fax it back to the trial coordinating centre. The trial management system will prompt them to do so via email and/or fax until the fax is received.

6.3 Blinding

The patient, their families, the healthcare team including the pharmacist and anyone involved in outpatient assessments will be blinded to the treatment allocation.

7. PREMATURE WITHDRAWAL OF PARTICIPANTS

Patients or their personal legal representatives may choose to withdraw completely from the trial. If this happens, no further data will be collected on that patient. If the patient is willing we will record the reason for any such withdrawal. However, we will retain the data collected on that patient up to that point.

8. STOPPING TRIAL TREATMENT EARLY

Patients or personal legal representatives may decide that the patient will stop taking the allocated treatment or the patient may be advised to stop taking the treatment by their doctor. If this happens, the patient will continue to be followed up as per protocol and their data included in the primary analyses. The reason for stopping the treatment prematurely will be recorded in the patient's CRF. If treatment is stopped as a result of a SAE or SUSAR, the event will be reported as per protocol. Such cases are not regarded as premature withdrawals.

9. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

9.1 STUDY DRUG

Oxactin 20mg Capsules
Fluoxetine International Non-proprietary Name (INN): Fluoxetine

9.1.1 Study Drug Identification

MARKETING AUTHORISATION NUMBER(S)

PL19611/0017

9.1.2 Study Drug Manufacturer

The fluoxetine and placebo will be purchased from
Discovery Pharmaceuticals Ltd
The Old Vicarage, Market Place, Castle Donington, Derbyshire, DE74 2JB
Telephone: +44 (0) 845 2416616
Fax: +44 (0) 845 2419919

Medical Information Direct Line: 0
Medical Information e-mail: medinfo@discoverypharma.co.uk
Medical Information Fax: +44 (0)1256 775 569

9.1.3 Marketing Authorisation Holder

Niche Generics Limited, 1 The Cam Centre, Wilbury Way, Hitchin, Hertfordshire, SG4 0TW, United Kingdom

9.1.4 Summary of Product Characteristics

The summary of product characteristics is given in the Appendix 1. To access the latest electronic version please go to:
http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1472791964904.pdf

9.2 PLACEBO

This will comprise a matching capsule containing the same exipients as the active drug (i.e. lactose, cellulose, magnesium stearate, colloidal silica)

9.3 Labelling and Packaging

This will be managed by a commercial trials organisation who will:

- Purchase commercial fluoxetine 20mg capsules (Oxactin) or matching placebo capsules. Commercial capsules will be taken as QA reference sample.
- Insert 186 fluoxetine 20mg capsules (6 months supply) into labelled bottles with child-resistant tamper-evident lids with induction seals and containing desiccant
- Insert 186 placebo capsules into matching labelled bottles

9.4 Storage

A commercial trials organisation will:

- Store awaiting a client supplied despatch request.
- Carry out final QP batch release.
- On receipt of a client supplied despatch request, the trial organisation will select the correct patient supplies, QA check and despatch to the correct site via an approved courier.

9.5 Management and accountability of the trial drugs at Site

Prior agreement will be obtained from the pharmacy at each participating site for the drug to be received, stock controlled, stored and temperature monitored in accordance with the current SmPC and dispensed on receipt of a prescription and pack details.

9.6 Prescribing and Dispensing of the trial drug

Following randomisation an automated completed prescription will be generated by the trial system. This should be printed and signed by the PI or sub investigator prior to being sent to pharmacy.

For inpatients, a doctor will prescribe the trial medication on the patient's medication chart giving the study name and patient /treatment code (see randomisation). The medication should be prescribed as "FOCUS trial medication (Fluoxetine 20mg OR placebo)", one capsule daily, oral (or enteral tube if the patient cannot swallow and an enteral tube is in place). For patients who are unable to swallow the capsule, but who do not have a feeding tube, the capsule may be opened and the contents mixed with a small volume of thickened liquid or liquefied food.

The hospital pharmacist will then dispense 6 months supply of study medication (186 capsules). When the patient is discharged from hospital the Trial medication will be continued and documented on the discharge summary.

9.7 Return of unused trial drug

9.7.1 From the patient

The patients will be asked to return any bottles containing unused capsules to the trial coordinating centre in a FREEPOST envelope along with their completed 6 month follow up form. The returned capsules will be counted to provide an estimate of adherence to the trial medication and then destroyed.

9.7.2 From hospital pharmacies

If a patient stops taking the trial medication or dies during hospital admission:

- the treatment pack should be returned to the local Pharmacy for reconciliation and destruction.
- Pharmacy staff should count the number of capsules remaining in the bottle and update the **IMP Accountability Log** in the Pharmacy Site File against the corresponding dispensing entry and dispose of the returns as per local protocol.
- Complete a FOCUS **Unused Patient Trial Medication and Confirmation of Destruction Form** and FAX to the trial co-ordinating centre on 0131 242 7742.

9.8 DOSING REGIME AND ADMINISTRATION

Patients will be prescribed the study medication (FOCUS trial Medication: 20mg capsule of fluoxetine or placebo capsule) to be taken daily at a time which is likely to maximise their adherence i.e. linked to an activity of daily activity. If the patient is unable to swallow capsules and has a nasogastric (NG) or other enteral feeding tube in place then the capsules may be broken open and put down the enteral feeding tube in accordance with the instructions given in the Handbook of drug administration via enteral feeding tubes (White & Bradnam 2010) If the patient has problems swallowing the capsules, but does not need an enteral feeding tube then the content of the capsules may be mixed with a small volume of thickened liquid or liquefied food.

9.8.1 PARTICIPANT ADHERENCE

Adherence to the trial medication will be monitored and recorded during the period of hospital admission for those enrolled as inpatients by the local research team. If the patient is moved to another hospital or unit the local research team should ensure that the medication and discharge pack goes with the patient and that instructions are given to prescribe the medication as per protocol. Once the inpatient has been discharged, or for outpatients, monitoring of adherence for the remainder of the treatment period will rely on self reporting by the patient or their proxy and on counting any remaining capsules returned to the trial co-ordinating centre at the end of the treatment period.

To increase the likelihood that patients will receive as much of the allocated trial medication as possible we will:

- Encourage the randomising clinician to emphasise the importance of taking the allocated medication regularly.

- Write to the GP shortly after enrolment to alert them to the patient's participation in the trial, the potential for drug interactions, the possible approaches to treating depression they diagnose and asking them to inform us of any suspected adverse reactions to the trial medication.
    - Send a fax alert to the GP shortly after discharge to remind the GP that the patient is participating in the trial; that the patient should have been supplied with all of their trial medication; that this trial medication will be either be placebo or fluoxetine. Note that whilst this is primarily for safety reasons (to ensure that the GP does not inadvertently prescribe fluoxetine in addition to the IMP) this will also serve as a reminder that the patient is in the trial.

- Make a courtesy telephone call to the patients (or relative/care staff if patient has incapacity) shortly after their discharge from hospital to ensure that the patient has the trial medication, that they have been given the details of the 24 hour help line, and that they have been told that they can contact us at any time about the trial if they have any questions.

- Write to the patient at home (3 months after enrolment) reminding them of the purpose of the FOCUS trial and the importance of adhering to the medication if possible. We will provide them with the means to feedback (by post, telephone or web) any concerns which we would respond to via their general practitioners.

Given the complexities of conducting a trial in our target population where adherence cannot be fully monitored once the patient is discharged from hospital, we fully anticipate that data concerning adherence will be incomplete. In the event that the trial fails to show a difference in outcomes between the active and placebo arms the data will provide a guide to whether poor adherence might contribute to the lack of effect. Providing we strive to attain those levels of adherence which would be achieved if fluoxetine was known to be effective, the results of the trial will be externally valid.

9.8.2 OVERDOSE

We are providing participants with a six month supply of trial medication which might be fluoxetine. There is a small risk that the patient, or someone close to them, may intentionally or accidentally take a large number of the capsules. This risk is much lower than in clinical practice where fluoxetine is given to treat depression. We will minimise this risk by: excluding patients with any history of overdose or attempted suicide and distributing capsules in bottles with child-resistant tamper-evident lids. .

If a person was to take a large number of the trial capsules then there is obviously only a 50% chance that the capsules would contain any active ingredient. The SmPC highlights that cases of overdose of fluoxetine alone usually have a mild course and that fatalities are extremely rare. It includes details of possible symptoms of overdose and advice regarding its management.

9.8.3 STOPPING THE TRIAL DRUG

Sudden cessation of an SSRI may lead to a withdrawal syndrome characterised by symptoms including headache, anxiety, restlessness, insomnia, headache and tremor). However, of all the SSRIs, fluoxetine has the longest half life (4-5 days) and therefore a withdrawal syndrome is very uncommon and tapering of the dose (especially from only 20mg od) is not regarded as necessary (NICE 2009).

9.9 OTHER MEDICATIONS

9.9.1 Permitted Medications

Diagnosis and treatment of depression during follow up in FOCUS trial.
A new diagnosis of depression, a diagnosis leading to referral for a specialist assessment, a diagnosis confirmed by a psychologist or psychiatrist or severe enough to require treatment with an antidepressant are a secondary outcome in the trial. Our hypothesis is that new depression will be less commonly diagnosed and treated in the group allocated fluoxetine. We will ascertain cases of depression by:

- Asking about a diagnosis or initiation of an antidepressant during hospital admission or during the first month– this will be recorded on the locally completed discharge form or the 1 month central follow up form
- Asking the General practitioner at 6 months and 12 months
- Asking the patient (or their proxy) at 6 months and 12 months

Since the primary question addressed by the FOCUS trial is whether an SSRI (fluoxetine 20mg od) enhances recovery from stroke it would be an advantage if the control group were kept free from any SSRIs including fluoxetine. However, it would be unethical to deny patients in the trial access to effective antidepressant treatment. We would therefore ask collaborating clinicians and the patients' GPs to adhere to the following treatment guideline:

If a patient in the FOCUS trial is diagnosed as having depression (or pathological emotionalism) which the responsible clinician judges to be severe enough to justify treatment with antidepressant drugs we would recommend that if possible they should avoid any SSRIs and prescribe either Mirtazapine or Trazodone. Both drugs are compatible with fluoxetine (there are no common or important interactions) although since Mirtazapine has some serotonergic activity there is likely to be a slightly greater risk of precipitating a serotonergic syndrome. Both drugs are recommended by NICE for treatment of depression in patients with physical illness (NICE 2009). The clinician might alternatively use a tricyclic antidepressant of their choice. Patients taking the trial drug and another antidepressant should be monitored carefully (e.g. check plasma sodium levels to exclude hyponatraemia) to identify any potential interactions.

If none of these approaches are judged suitable for a patient then the clinician could treat with an SSRI including fluoxetine 20mg od (since a dose of 40mg per day – the total amount a patient in the active treatment arm would be receiving – is regarded as a reasonable treatment of depression). However, this approach may make it more difficult to identify any treatment effect in the trial.

9.9.2 Prohibited Medications

Mono Amine Oxidase Inhibitor (MAOI) antidepressants (e.g. phenelzine, procarbazine, tranylcypromine, isocarboxazid) and those used for Parkinsons disease (e.g Selegiline) have potentially dangerous interactions with fluoxetine and should therefore if at all possible be avoided. If they have to be used then the patient's trial medication must be stopped at least 5 weeks before starting a MAOI.

Metoprolol used in heart failure. The risk of metoprolol adverse events including excessive bradycardia, may be increased because of an inhibition of its metabolism by fluoxetine.

Although, not prohibited the potential for interactions with other groups of medications including aspirin, NSAIDs, Warfarin should lead to close monitoring, at least initially.

10. STUDY ASSESSMENTS AND DATA COLLECTION

The Principal Investigator, and researchers on each site, will collect the ***local*** data listed in the schedule of study assessments below. The Chief Investigators and the research team in the central coordinating office will collect the ***central*** data (see schedule below).

10.1 Study Assessment Schedule

	Days	Weeks							
Assessment	2-15	4-6	12	24	26	30	50	52	54
Local									
Screen of eligibility	x								
Check results of post stroke bloods	x								
Give PIB to patient and/or carer	x								
CONSENT	x								
Collect baseline data	x								
Randomise	x								
Record treatment code/study no.	x								
Prescribe study medication	x								
Dispense 6 months of treatment	x								
FAX no. of dispensed medication	x								
Complete discharge form including		+							
Adverse events		+							
All medications		+							
Adherence		+							
Updated contact details		+							
Central (postal or telephone)									
Email/fax notification of allocation	x								
Letter informing GP of participation	x								
1 month follow up for outpatients		o							
Send fax alert following discharge to GP of patient participation.		x							
Courtesy Call to participant		x							
3 month prompt to patients			x						
GP Questionnaire							x		
Adverse events		o		x					
Follow up on previous AEs				x			x		
All medications		o		x			x		
Adherence		o		x					
Resource use				x			x		
Patient follow up									
Adverse events		o			x				
Follow up on previous AEs					x			x	
Adherence		o			x				
modified Rankin scale					x			x	
Stroke Impact Scale					x			x	
Mental health inventory 5					x			x	
EQ5D-5L (HRQOL)					x			x	
SF36 Vitality subscale					x			x	
Resource use					x			x	
Retrieve residual capsules (pill count, reconciliation and destruction)					x				
email newsletters to patients regularly			x						x

+ - only for patients enrolled as inpatients

o - only for patients enrolled as outpatients

10.2 STUDY SAFETY ASSESSMENTS

Our monitoring system will primarily be aimed at identifying **S**uspected **U**nexpected **S**erious **A**dverse **R**eactions (SUSARS) but also identifying whether the frequency of **S**erious **A**dverse **R**eactions is greater than in other populations given fluoxetine and sufficiently common to offset any benefits. We do not aim to detect the occurrence of the very many adverse events which occur in stroke patients and which are very unlikely to be related to participation in the trial or the medication.

The trial materials given to the patient, and/or their carer will contain details of the known adverse reactions to fluoxetine (based on the SmPC) and the common adverse events which occur after stroke. They will receive a diary in which they are encouraged to record the date and nature of any adverse events.

Patients enrolled whilst an inpatient will have a hospital discharge form completed by the local coordinator at the time of discharge from the recruiting centre, or shortly after. The data collected will be entered on a secure web based form or faxed to the coordinating centre to ensure that we are alerted to any important **A**dverse **R**eactions. If no discharge form is received by 6 months, then it will be assumed that the patient is still in hospital and the local research team will be asked to provide information concerning adherence, adverse events, non IMP medications and outcomes.

Patients enrolled whilst an outpatient will have a central follow up at one month after recruitment to detect Adverse Reactions.

At 12 weeks after randomisation the trial co-ordinating centre will mail a postal reminder to the patients to report any adverse events or difficulties with the trial medication.

All surviving patients will be followed up at 6 and 12 months after randomisation, whether they adhered to their allocated treatment or not. At each follow up the GP will be asked about adverse events. In order to detect **A**dverse **R**eactions between the scheduled follow ups a system will be in place to allow the patients, their carers or their GPs to report any adverse reactions to us via:.

- Post – freepost envelope and Adverse Events form to return to us with details of any adverse reactions the patient has experienced
- Helpline – telephone phone number which will allow the patients or their doctors to either leave a message (if non urgent) or to access a Trial Doctor (if urgent).
- Web – secure website where they can record any adverse effects, ask for advice etc.

10.3 CENTRAL FOLLOW UP

About 2 weeks before any central follow up is due the trial co-ordinating centre will contact the General Practitioners (or Hospital Co-ordinators if no discharge form has been received) to check that the patient is alive and that they may be approached for follow-up. The GP will be asked (and paid a fee) to provide a list of non-IMP medications, information regarding the patient's adherence to the IMP, details of any adverse events, hospital admissions and up to date contact details for the patient.

If appropriate, the trial co-ordinating centre will then mail a postal questionnaire to the patient at 4 weeks (only for those recruited as outpatients), 26 weeks and 52 weeks The patient will also be given the option of completing the follow-up questionnaire on-line (via a secure web interface) which will provide online help and data validation. If the patient does not respond to the postal questionnaire they will be telephoned. The questionnaire at 26 and 52 weeks aims to capture the primary and secondary outcomes and includes the outcome of any adverse events which have been reported earlier in the follow up. If the patient has incapacity, the next of kin (proxy) will be asked to complete and return the forms. If the patient is unable to speak English we will ask that their carer supports them in filling out the forms. If the follow up information cannot be obtained by either the postal or telephone questionnaire the local research team may be asked to arrange a face-to-face follow up at a clinic or home visit.

Experience in previous trials indicates that failure to complete a postal questionnaire usually indicates a failure of receipt or inadvertent non-completion rather than a wish not to participate further in the trial. Central follow-up (telephone or postal) has been found to be cost-effective and efficient. If a patient dies after a hospital follow-up or one month form has been completed and within 6 months of randomisation, the clinician can conveniently inform the FOCUS Trial Office by completing an on line form or a postal form. Ascertaining the precise date of death will be very important for survival analyses.

10.3.1 Data Linkage and Extract to determine outcome and longterm survival

We plan to use The Health and Social Care Information Centre and other central UK NHS bodies to obtain information about the health status and resource use of participants to determine outcomes and long term survival until the end of the trial and beyond. There is evidence that functional outcome at 6 months post stroke is strongly associated with longterm survival (Bruin 2008). Therefore, if fluoxetine treatment is associated with improvements in functional status at 6 months it would be important to establish whether this translates into longer survival.

11. STATISTICS AND DATA ANALYSIS

11.1 SAMPLE SIZE CALCULATION

We are planning to enrol at least 3000 patients in the main phase of FOCUS. This will provide 90% power to detect a 5.6% absolute increase in percentage with mRS 0-2 from 27.0% to 32.6% based on an ordinal analysis which is statistically more efficient than an analysis which dichotomises the mRS (OAST 2007). If FOCUS and AFFINITY combined enrol 4500 this will provide 90% power to detect a 4.6% absolute improvement in percentage with mRS 0-2 from 27.0% to 31.6%.

In arriving at our sample sizes we have tried to take account of the effect sizes seen in the FLAME trial alongside the effects which clinicians, and their patients would find interesting. Since fluoxetine is safe and inexpensive, the FOCUS trial seeks reliably to detect the moderate, but nonetheless clinically important benefits that might be associated with widespread use of fluoxetine in this population. However, we also need to take account of the feasibility of enrolling large numbers of patients into the FOCUS trial.

We have based our expected outcomes for our placebo group on the distribution of mRS score measured at 6 months after randomisation in the CLOTS trials which evaluated graduated compression stockings (CLOTS 2009). The CLOTS trials enrolled hospital admitted stroke patients (the great majority from hospitals in the UK), who had a stroke severe enough to

render the patients immobile on the day of randomisation (Day 0-3 of admission). CLOTS trials 1 & 2 combined recruited 5632 patients of whom 5419 had a mRS [score missing in 213 patients]. Of those where the information was present the following table shows the breakdown of scores

	CLOTS trials 1 & 2		FLAME trial	
Modified Rankin	No.	%	No.	%
0	196	3.6	0	0
1	470	8.7	4	3,5
2	837	15.5	16	13.9
3	1164	21.5	44	38.3
4	616	11.4	43	37.4
5	889	16.4	6	5.2
6	1247	23.0	2	1.7
Total	5419		115	

There were more good outcomes in CLOTS than in the FLAME trial but this may be because, in FLAME, the mRS was measured at only 3 months. In CLOTS, however there were many more deaths and very poor outcomes. This may suggest that the CLOTS trials enrolled a much broader range of stroke severities than in FLAME. In FOCUS we also aim to enrol a much broader range of patients than in FLAME.

Sample size estimate based on proportion with mRS of 0-2

In CLOTS 1&2, 27% of patients had a mRS of 0-2. Based on this, the following table shows the number of patients needed per group to show the absolute differences in proportions from 10% to 4% based on a two-sided, two-sample test with a 5% level of significance and a 90% power.

Sample size table 1 – based on dichotomised outcomes of CLOTS trial data

Absolute difference in proportion mRS0-2	**10%**	**9%**	**8%**	**7%**	**6%**	**5%**	**4%**
Group 1 proportion	0.27	0.27	0.27	0.27	0.27	0.27	0.27
Group 2 proportion	0.37	0.36	0.35	0.34	0.33	0.32	0.31
Odds ratio	1.59	1.52	1.46	1.39	1.33	1.27	1.22
No. per group	475	580	726	936	1257	1786	2753
Total sample size required	**950**	**1160**	**1452**	**1872**	**2514**	**3572**	**5506**

The patients recruited into the CLOTS trials had to be immobile and as such the figures obtained from this sample may be more extreme than we may see in FOCUS. In FOCUS we will enrol some outpatients and some patients without deficits which cause immobility. In case 27% in one group is not realistic the following table repeats the same information however this uses 50% mRS 0-2 and shows the samples sizes required to show an absolute differences of the range from 10% to 4%.

Sample size table 2 – based on dichotomised outcomes

Absolute difference in proportion mRS0-2	**10%**	**9%**	**8%**	**7%**	**6%**	**5%**	**4%**

Group 1 proportion	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Group 2 proportion	0.60	0.59	0.58	0.57	0.56	0.55	0.54
Odds ratio	1.50	1.44	1.38	1.33	1.27	1.22	1.17
No. per group	538	664	839	1094	1486	2134	3327
Total sample size required	**1076**	**1328**	**1678**	**1188**	**2972**	**4268**	**6654**

Sample size estimate based on ordinal logistic analysis

Using the ordered categorical data method described by Machin (2008), and discussed at the following address http://www.childrens-mercy.org/stats/weblog2004/OrdinalLogistic.asp, we have built the excel sheet illustrated below which calculates the sample size required. The cells shown in grey are the parameters which must be specified to calculate the sample size: the numbers in each category, power, significance level, 1 or 2 sided and also the common odds ratio.

Sample size table 3. Excel spreadsheet to calculate sample size based on ordinal analysis

Modified Rankin		0	1	2	3	4	5	6	Total
CLOTS (n)		196	470	837	1164	616	889	1247	5419
Control	Probability	0.036	0.087	0.154	0.215	0.114	0.164	0.230	
	Cumulative probability [Cp]	0.036	0.123	0.277	0.492	0.606	0.770	1.000	
	Cumulative odds [CCO] (Cp/(1-Cp))	0.038	0.140	0.384	0.969	1.537	3.346		

Treatment	common odds ratio [COR]	1.2							
	Cumulative odds [TCO] (CCO*COR)	0.045	0.168	0.461	1.163	1.844	4.015		
	Cumulative probability	0.043	0.144	0.315	0.538	0.648	0.801	1.000	
	Probability	0.043	0.101	0.171	0.222	0.111	0.152	0.199	
Combined	Cumulative odds ratio	0.833	0.833	0.833	0.833	0.833	0.833		
	Pi bar	0.040	0.094	0.163	0.219	0.112	0.158	0.215	
	Pi bar cubed	0.000	0.001	0.004	0.010	0.001	0.004	0.010	
Sample size parameters	Alpha	0.05		Z alpha	1.96				
	No. sides	2		Z beta	1.28				
	Power	0.9							
	n	1957							

Using the number of patients observed in CLOTS 1 & 2 to give an estimate of the distribution of cases across the categories of the mRS and a common odds ratio of 1.2, a two-sided 5% level of significance and a 90% power we would need 1957 patients per group, 3914 in total.

The OAST collaboration estimated, based on analyses of completed stroke trials (OAST 2007), that by using an ordinal analysis of the mRS one can maintain the same power whilst reducing the sample size by approximately 25%. 3914 is approximately 71% of the sample size required to show an odds ratio of 1.2 using the binary calculation n=5506, shown in the column labelled 4% absolute difference in the first sample size table above.

Keeping all other parameters constant the following table shows the samples sizes required to detect common odds ratios from 1.1 to 1.5.

Sample size table 4 – based on ordinal analysis of mRS

Common Odds Ratio	Sample Size (both groups combined)
1.1	14332
1.2	3914
1.3	1888
1.4	1148
1.5	790

A trial of 3000 will provide 90% power to detect a 5.6% absolute increase in percentage with mRS 0-2 from 27.0% to 32.6% based on the ordinal analysis. 4500 (from FOCUS plus AFFINITY or EFFECTS) would provide 90% power to detect a 4.6% absolute improvement in percentage with mRS 0-2 from 27.0% to 31.6%.

The trial steering committee (TSC) will review the target sample size and adjust this based on:

- Advice from the DMC
- Accruing data on
    - the enrolment into specific pre-specified subgroups
    - completeness of follow up
    - distribution of mRS categories in the population of enrolled subjects (i.e. both treatment groups combined), overall and in specific patient categories (e.g. those with motor deficits, aphasia, etc)

For example, if the distribution of mRS is different to that anticipated, then the sample size might need to be increased. This approach has the advantage that such sample size adjustments can be made without reference to the accumulating blinded data, and avoids the need for conditional power calculations which can be unreliable.

11.2 PROPOSED ANALYSES

Our primary analyses will retain patients in their original assigned treatment groups.

Our primary analysis will compare the mRS at the six month follow up using an ordinal analysis adjusted in those factors included in our minimisation algorithm.

We will compare the mRS at the twelve month follow up to establish if any benefits observed at 6 months are maintained.

Secondary analyses will compare the two treatment groups with respect to the following outcomes at 6 and 12 months.

- Survival (Logistic regression)
- EQ5D-5L (HRQOL) to generate utilities
- SIS (for each of 9 domains on which the patient scored 0-100)
- MHI 5 (mood)
- Fatigue (Vitality subscale of SF36)
- New diagnosis of depression requiring treatment with antidepressants
- Adverse events
- Adherence to trial medication

Longer term survival will be analysed with Cox proportional hazards model

We will also perform analyses of potential mediating factors e.g. the role of depression. We will seek to answer the question whether any benefits are mediated by improvement in mood (based on MHI 5 and also whether any apparent loss of benefits in mRS or SIS between 6 months to 12 months is because of a deterioration in mood.

11.2.1 Pre-defined subgroups

The mRS will be compared at six months with an ordinal analysis in the following subgroups:

- Age (≤70, > 70yrs)

- Baseline probability of a good outcome on mRS (Counsell 2002) – to see if effects remain constant across the range of stroke severities (<0.15 vs 0.15-1 probability of being alive and independent at 6 months)
- Ischaemic vs haemorrhagic stroke
- Patient who were unable to consent for themselves since this subgroup will allow us to answer the question whether routine use of fluoxetine is likely to benefit patient in whom a formal assessment of mood is impossible because of communication and cognitive problems.

In addition we are particularly interested to know whether the effect of treatment on neurological function is modified by specific neurological deficits present at baseline. Because patients may have a combination of neurological deficits, individual patients may appear in more than one subgroup

Patients with a motor deficit (i.e. weakness or clumsiness on NIHSSS) affecting face, arm or leg.
- Relevant outcomes – SIS – Strength, mobility, hand/arm function

- Patients with aphasia based on the NIHSS

- Relevant outcomes – SIS – communication

We envisage that levels of missing data in the primary outcome will be exceedingly low from previous experience of acquiring the mRS by postal and telephone questionnaire and the primary analysis will be a complete case analysis. If we see higher levels of missing data than expected, we will use a suitable analysis, based on the likely missing data mechanism. We will consider whether to extend missing data methods to secondary outcomes at a blinded review of the Statistical Analysis Plan immediately before database lock."

A detailed analysis plan will be developed and reported by the chief investigators and an independent statistician prior to the database being locked at the end of follow up for final analysis.

11.2.2 Economic analysis.

Within trial economic analysis of direct resource costs and health outcomes will be conducted on an intention to treat basis. A NHS perspective will be adopted for measuring and valuing health service use. We will estimate one year cumulative costs of in-patient episodes, hospital clinic visits, and health service use within primary care settings. Self-reported health at baseline (where possible) and at 6 and 12 months of follow up will be measured using the EuroQoL (EQ5D-5L) preference based scale. We also plan to validate the EQ5D-5L by checking the concordance with the modified Rankin score. Survival times will be adjusted using the EQ5D-5L to calculate quality adjusted life years (QALYs). The primary treatment effect in the economic analysis will be estimated using a regression model for incremental costs and incremental QALYs. Multiple imputation will be used to address missing values. The distribution of predicted and expected incremental cost effectiveness will be examined using bootstrapping of key cost and outcome parameters and the heterogeneity of treatment effects will be assessed using pre-defined strata. Longer run modelling of incremental costs and health outcomes will estimate the distribution of costs and QALYs calculated over the expected patient lifetimes.

12. ADVERSE EVENTS

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

12.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward or unintended response to an IMP which is related to any dose administered to that participant.

An **unexpected adverse reaction** (UAR) is an adverse reaction that is not consistent with the applicable product information for the IMP, e.g. the Investigator Brochure (IB) for a non licensed IMP or the SmPC for a licensed product.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR) or **suspected unexpected serious adverse reaction** (SUSAR) is any AE, AR or UAR that at any dose:

- results in death;
- is life threatening* (i.e. the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- requires inpatient hospitalisation or prolongation of existing inpatient hospitalisation
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect.

* Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

Any hospitalisation that was planned prior to randomisation will not meet SAE criteria. Any hospitalisation that is planned post randomisation will meet the SAE criteria.

12.2 Assessment of AEs

12.2.1 Assessment of Seriousness

Each AE must be assessed for seriousness, causality, severity and expectedness by the Principal Investigator or another suitably qualified physician in the research team who is trained in recording and reporting AEs and who has been delegated this role. For randomised double blind studies, AEs will be assessed as though the trial participant was taking the IMP.

The Investigator will make an assessment of seriousness (as defined in section 12.1)

12.2.2. Assessment of causality

The Investigator will also make an assessment of whether the AE is likely to be related to the IMP according to the following definitions:

Unrelated: where an event is not considered to be related to the IMP.

Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.

Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

Where there are two assessments of causality, for example, the Investigator and the

Sponsor assessment, or the CI and Investigator assessment, the causality made by the Investigator cannot be downgraded. In the case of a difference of opinion, both assessments are recorded and the 'worst case' assessment is used for reporting purposes.

12.2.3 Assessment of Severity

The Investigator will make an assessment of severity for each AE and this should be recorded on the CRF or AE form according to the following categories:

Mild: an event that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.
The term 'severe' used to describe the intensity of an event should not be confused with the term 'serious', as defined in section 5.1, which is a regulatory definition based on trial participant/event outcome action criteria. For example, a headache may be severe but not serious, while a minor stroke may be serious but is not severe.

12.2.4 Assessment of Expectedness

If the AE is judged to be related to the IMP, the Investigator will make an assessment of expectedness based on knowledge of the reaction and any relevant product information as documented in the Summary of Product Characteristics (SmPC). The event will be classed as either:

Expected: the reaction is consistent with the toxicity of the study drug listed in the SmPC.

Unexpected: the reaction is not consistent with the toxicity listed in the SmPC.

12.3 FLUOXETINE

Fluoxetine is a well established drug which has been used for more than 20 years in the treatment of depression, and other related problems and has a well established safety profile. It has been used to treat depression and emotionalism in many thousands of patients worldwide.

12.3.1 Known Side Effects of Fluoxetine

The Summary of Products Characteristics revised 24/07/2015 (see Appendix 1) records that Fluoxetine can cause a variety of side-effects. Please refer to the tabulated list of adverse reactions in section 4.8 Undesirable effects of the SmPC in Appendix 1 below

These side effects are expected in this patient population and will NOT be reported to the ACCORD office within 24 hours, even in situations where these expected events fulfil the criteria of serious (as defined in section 12.1) of the trial protocol.

12.3.2 Class Effects Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and tricyclic antidepressants. The mechanism leading to this risk is unknown.

The frequency of some adverse events may be affected by the Fluoxetine. A cohort study of more than 60,000 patients aged 65 years (Coupland et al 2011) or more who were diagnosed with depression and followed up found that 764,650 prescriptions for SSRI antidepressants were issued and that SSRIs were associated with significantly higher rates of:

- all cause mortality (adjusted hazard ratio 1.54; 95% confidence interval 1.48 -1.59)
- stroke/TIA (1.17;1.10-1.26)
- myocardial infarction (1.15; 1.04 -1.27)
- upper gastrointestinal bleeding (1.22; 1.07- 1.40)
- serious falls (1.66; 1.58 -1.73)
- serious fractures (1.58; 1.48 -1.68)
- epilepsy/seizures (1.83; 1.49 - 2.26)
- attempted suicide/self harm (2.16; 1.71 - 2.71)

hyponatraemia (1.52; 1.33 to 1.75)

12.4 Pre-specified outcomes

Death, life-threatening complications and prolonged hospital stay are pre-specified outcomes to be reported in this trial and also to the independent DMC.

Stroke is a serious medical condition where medical complications are common and poor outcomes frequent. About 20% of hospitalized patients would be expected to die in the first month after a stroke and another 10% by the end of the first year. Up to a third will develop a chest or urinary infection whilst in hospital, perhaps 5% will develop clinically apparent venous thromboembolism, epileptic seizures or gastrointestinal bleeding. Many patients fall, and some sustain injury.
Therefore adverse events, many of which would be categorised as serious (as per the definitions in section 10.1), are likely to be frequent in the FOCUS trial.

This clinical trial is using a drug which is in common use. It is important to consider the natural history of the critical medical event affecting each patient enrolled, the expected complications of this event, and the relevance of the complications to Fluoxetine.

12.5 ADVERSE EVENT REPORTING FOR THIS TRIAL

12.5.1 You should NOT report to the Trial Co-ordinating Centre:

Any Adverse Events that are part of the natural history of the primary event of stroke or expected complications of stroke (even if they fall under the category of Serious as defined in Section 10.1) should **NOT** be reported to the trial office or the trial sponsor These include:

- Chest infections
- Urinary infections
- Other infections including those of soft tissues
- Renal dysfunction
- Painful shoulder syndromes
- Pressure sores
- Spasticity or contractures
- Any other known complications of stroke

Reporting these events is unlikely to be informative and places an unnecessary burden on the local researchers which would compromise the practicality of this investigator lead trial.

12.5.2 You SHOULD report to the Trial Co-ordinating Centre

- The following Adverse Events should be reported to the Trial Co-ordinating Centre on the discharge form. These events will also be collected during the 6 months of follow-up when the patient is taking the medication providing they meet the criteria of a Serious Adverse Event as defined in section 12.1.
- all cause mortality
- stroke/TIA
- myocardial infarction
- upper gastrointestinal bleeding
- serious falls
- serious fractures
- epilepsy/seizures
- attempted suicide/self harm
- hyponatraemia

We believe that this systematic approach will be more informative than relying on adhoc Adverse Event reporting. These data will be presented to the DMC.

We will also systematically collect information on hospital admissions and new medications which will provide an additional alerting system – e.g. if patients are commenced on a new anticonvulsants, antidepressants etc.

12.5.3 You MUST report to the Trial Sponsor

All other SAEs which are not listed in this protocol or on the SmPC are classed as 'reportable SAEs' and will be reported to the ACCORD office within 24 hours of the CI or PI becoming aware of the event, as described in section 12.5.4 of the protocol.

12.5.4 Reporting SAEs/SARs/SUSARs to the Trial Sponsor

Once the Chief or Principal Investigator becomes aware that any 'reportable' SAE/SUSAR has occurred in a study participant, they must report the information to the ACCORD Research Governance & QA Office within 24 hours. The SAE/SUSAR form must be completed as thoroughly as possible with all available details of the event, signed by the Investigator or designee. If the Investigator does not have all information regarding an SAE/SUSAR, they should not wait for this additional information before notifying ACCORD. The form can be updated when the additional information is received.

The SAE/SUSAR report must provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.4, Assessment of Expectedness.

The SAE/SUSAR form should be transmitted by fax to ACCORD on +44 (0)131 242 9447 or may be transmitted by hand to the office.

Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information until this is supplied.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF). Any reported SAE (to Sponsor) should be followed up to resolution.

12.6 SPONSOR REGULATORY REPORTING REQUIREMENTS

The ACCORD Research Governance & QA Office is responsible for Pharmacovigilance reporting on behalf of the co-sponsors (Edinburgh University and NHS Lothian).

The ACCORD Research Governance & QA Office has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

The Trial Co-ordinating Centre will inform Investigators at participating sites of all SUSARs and any other arising safety information. In the event that any safety information is sent directly to the trial co-ordinating centre it must to forwarded to ACCORD.

A Developmental Update Safety Report (DSUR) will be submitted to the regulatory competent authority and main REC listing all SARs and SUSARs. SUSARs for this trial will include the treatment allocation.

12.7 Need Advice?

Advice for investigators on reporting of adverse events is available in the trial manual, on the trial website and via our 24 hour telephone helpline.

12.8 Emergency Unblinding Procedures for this study

If a contraindication to fluoxetine develops after randomisation, e.g. need for treatment with a MAOI drug, the trial treatment should simply be stopped and all usual standard care given. Unblinding should be done only in those rare cases when the clinician believes that clinical management depends importantly upon knowledge of whether the patient received fluoxetine or placebo. In those few cases when urgent unblinding is considered necessary, the doctor caring for the patient will be instructed to call the 24 hour helpline. The doctor will then access a secure website to find out whether the patient received fluoxetine or placebo. An unblinding report form should be completed by the doctor and sent to the Trial Coordinating Centre (TCC) within one working day.

In the event of a SUSAR, ACCORD will have the facility to allow them to unblind the patient prior to expedited reporting to the ethics committee and competent authority.

13. PREGNANCY

Pregnancy is not considered an AE or SAE, however, the Investigator must collect pregnancy information for any female participants who become pregnant while participating in the study. The Investigator should record the information on a Pregnancy Notification Form and submit this to ACCORD within 14 days of being made aware of the pregnancy.

All pregnant female participants should be followed up until after the birth or otherwise (i.e. spontaneous termination) to allow information on the status of the mother and child to be reported to ACCORD.

14. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

14.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group. Professor Martin Dennis and Professor Gillian Mead (Joint Chief Investigators and Principal Investigators in two participating sites) Karen Innes (Trial Manager), Cat Graham (Trial Statistician).

14.2 TRIAL CO-ORDINATING CENTRE (TCC)

The TCC is responsible for all aspects of the management of the FOCUS trial and is based at the Centre for Clinical Brain Sciences at Edinburgh University. Responsibilities include: Regulatory Submissions and compliance; Financial Management; Monitoring of Sites; Training; Patient Information and Communication; Endpoint assessment; Data Collection Systems and Data Management; IMP Management; Statistical Analysis; Reports and Publications and Archiving of the TMF in accordance with funder and sponsor requirements.

14.3 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details will be agreed in advance of its first meeting.

14.4 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. During the period of recruitment into the study, interim analyses of the baseline and follow up data will be supplied, in strict confidence, to the chairman of the data monitoring committee, along with any other analyses that the committee may request. In the light of these analyses, the data monitoring committee will advise the chairman of the steering committee if, in their view, the randomised comparisons have provided both (i) 'proof beyond reasonable doubt' that for all, or some, the treatment is clearly indicated or clearly contra-indicated and (ii) evidence that might reasonably be expected to materially influence future patient management. Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but the DMC will work on the principle that a difference of at least 3 standard errors in an interim analysis of a major outcome event (e.g. death from all causes or independent survival at six months) may be needed to justify halting, or modifying, a study before the planned completed recruitment. This criterion has the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule is proposed. Following a report from the DMC, the steering committee will decide whether to modify entry to the study (or seek extra data). Unless this happens however, the steering committee, the collaborators and central administrative staff will remain ignorant of the interim results.

The terms of reference of the Data Monitoring Committee, the DMC Charter and the names and contact details will be agreed at the first meeting of the DMC. The Chairs of the DMCs of FOCUS, AFFINTY and EFFECTS will communicate regularly to share any concerns about the accruing data and will share data if indicated. Therefore the DMC will potentially have access to all available information when making its recommendations. This aims to maximise patient safety.

14.5 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring, audits, REC review, and regulatory inspection(s). In the event of an audit, the Investigator agrees to allow the sponsor, representatives of the sponsor or regulatory authorities direct access to all study records and source documentation.

14.6 RISK ASSESSMENT

An independent risk assessment of the trial and its procedures has been carried out by an ACCORD Clinical Trials Monitor to determine the level of monitoring. An independent risk assessment will also be carried out by the ACCORD Quality Assurance Group to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

14.7 STUDY MONITORING

GCP section 5.18.3 states in regard to monitoring that, *"the determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified."*

The FOCUS trial is a large, pragmatic, randomised double blind placebo controlled trial. The intervention (fluoxetine) has marketing authorisation since 1988 and has been in therapeutic use for the management and treatment of; major depressive episodes; obsessive-compulsive disorder; bulimia nervosa and moderate to severe depressive episodes in children and adolescents. Its safety profile is now well established and few significant serious adverse events associated with its use have been identified.

The trial will routinely collect data on adverse events which may theoretically be associated with this product and the condition under investigation, and these will be reviewed by the independent Data Monitoring Committee (DMC). The trial procedures are based on routine clinical procedures and include (1) the administration of the trial drug using routine clinical use; (2) collecting routine clinical information from the medical records; and (3) informed consent. There are no complex procedures or interventions for the participants or investigators in this trial. Clinical management for underlying conditions will remain as per each hospital's standard protocol. Based on these factors, the probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in this research study is considered to be low in each of these categories The Monitoring Procedure to assure appropriate conduct of the trial will utilise 100% central data monitoring.

A risk assessment has been conducted by the Sponsor Monitor. Site monitoring will be followed in accordance with the Monitoring Plan.

14.7.7 Archiving of centre data

All trial related and source documents should be archived for fifteen years following the end of the trial. The costs for this must be discussed and agreed locally by each R&D department as part of the R&D approval process.

14.7.8 Archiving of central data

All trial related documents will be archived for 5 years in accordance with the Sponsor archiving policy unless an alternative longer archiving period is specified by the funder.

15. GOOD CLINICAL PRACTICE

15.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

A favourable ethical opinion will be obtained from the appropriate REC and local R&D approval will be obtained prior to commencement of the study.

15.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, and any relevant amendments.

15.3 PRINCIPAL INVESTIGATOR RESPONSIBILITIES

The Principal Investigator is responsible for the overall conduct of the study at the site and ensuring any person delegated responsibilities are fully informed, understand and are fully compliant with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriately trained member of study site staff. Responsibilities must not be delegated or duties undertaken until a CV, proof of current GCP certification and any other relevant training certificates have been collected and reviewed by the Principal Investigator and details of the person and their responsibilities clearly documented on the Delegation Log and signed by the Principal Investigator and those persons delegated responsibilities.

15.3.1 Confirming patient eligibility

Although a research nurse may be delegated the responsibility for identifying suitable patients, obtaining consent (see section 5.2) and randomising the patient, the PI or physician sub investigator must confirm in writing in the medical records that the patient fulfils the eligibility criteria and must sign the FOCUS trial prescription form for the trial medication.

15.3.2 Study Site Staff

The Principal Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

15.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

15.3.4 Principal Investigator Documentation

Prior to beginning the study, each Principal Investigator will be asked to provide particular essential documents to the Trial Co-ordinating Centre, including but not limited to:

- An original signed Principal Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV), signed and dated by the Principal Investigator indicating that it is accurate and current.

The Trial Co-ordinating Centre will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) and that appropriate documentation is available in local ISFs.

15.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training or undergo GCP training. This should be updated every two years throughout the trial or in accordance with local R & D protocol if more frequent.

15.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the sponsor, its designee, Regulatory Authorities, or the REC. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

15.3.7 Data Protection

All Principal Investigators and study site staff involved with this study must comply with the requirements of the Data Protection Act 1998 with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Access to collated participant data will be restricted to those clinicians treating the participants.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

15.3.8 Follow up

The PI is responsible for follow up of participants recruited as inpatients until hospital discharge or death (whichever occurs first) or, for participants recruited as outpatients, until the patient has been dispensed the trial medication. In exceptional circumstances, where central follow up has failed, the PI may be requested by the TCC to collect follow up data at 6 and/or 12 months.

16. STUDY CONDUCT RESPONSIBILITIES

16.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant, must be reviewed and approved by the Chief Investigator.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to participants being enrolled into an amended protocol.

16.2 PROTOCOL VIOLATIONS AND DEVIATIONS

Principal Investigators should not implement any deviation from the protocol without agreement from the Chief Investigator and appropriate REC, Regulatory Authority and R&D approval except where necessary to eliminate an immediate hazard to trial participants.
In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation should be recorded in the CRF. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

16.3 STUDY RECORD RETENTION

Each participating centre will be responsible for ensuring that all essential documentation are retained and archived locally in accordance with the trial protocol..

16.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors () must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and take the appropriate action.

Not every violation from the protocol needs to be reported to the regulatory authority as a serious breach. If the co-sponsors deem the incident to be a minor deviation from the protocol when identified, corrective and preventative actions will be taken where appropriate and they will be recorded in file notes, held within the TMF or ISF.

16.5 END OF STUDY

The end of study is defined as the last participant's last follow up.

The Investigators and/or the trial steering committee have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC and Regulatory Authority within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved.

A summary report of the study will be provided to the REC and Regulatory Authority within 1 year of the end of the study.

16.6 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

The IMP will not be continued beyond the 6 month treatment period in the FOCUS trial. The patients local GP or physician may choose to treat the patients with fluoxetine after the patient has stopped taking the IMP.

16.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been designed by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by
- poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the Sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities.
- Sites which are part of the United Kingdom's Nation Health Service will have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

17. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

17.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines. The success of this study depends entirely on the collaboration of a large number of doctors, nurses, pharmacists, other health professionals, patients and relatives. Those included in the Delegation Logs will be included in any listing of collaborators.. For this reason the credit for the main results will be given, not to the central trial coordinators, but to all wholehearted collaborators in the study. The primary trial publication will be drafted by a writing committee whose membership has been approved by the steering committee. The manuscript must be approved by the steering committee before submission for publication.

17.2 PUBLICATION

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

Co-ordinating centre (for all information and queries)
FOCUS Co-ordinating Centre, Centre for Clinical Brain Sciences (CCBS)
Room FU303
The University of Edinburgh
Chancellor's Building
49 Little France Crescent
Edinburgh
EH16 4SB
University of Edinburgh. email: focus.trial@ed.ac.uk, telephone: +44 (0)131 242 7741 fax: +44 (0)131 242 7742; web-site http://www.focustrial.org.uk

Steering committee
Trial Steering Committee will meet annually and the members will be made up of but not limited to the following:
Independent Chairman
Two Independent members
Co-Chief Investigators: Professor Gillian Mead, Professor Martin Dennis
Additional named grantholders
Lead Statistician: Dr Stephanie Lewis
Trial Manager: Karen Innes
Lay representative
Funding representative
Sponsor Representative

Management group
Professor Gillian Mead, Professor Martin Dennis, Karen Innes (Manager), Catriona Graham (Statistician)

Timelines
We expect to start enrolling patients into start up phase in July 2012. Assuming that this goes well, funding is identified and no major amendments are required to our protocol we would expect to start the main phase in 2014 and complete the trial by 2018.

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