ASSESSMENT OF FLUOXETINE IN STROKE RECOVERY (AFFINITY) TRIAL

**Formal title:** An Australian-lead, investigator-initiated, multi-centre, prospective, randomised, parallel group, double-blind, placebo-controlled trial to establish the effect(s) of routine administration of fluoxetine (20 mg once daily) in patients with recent stroke.

**Short title:** A multicentre randomised controlled trial to establish the efficacy of routine administration of fluoxetine in patients with a recent stroke.

**Trial Protocol**

Version 2, 31 May 2012
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Australian New Zealand Clinical Trial Registry number: ACTRN12611000774921
INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all the necessary details for carrying out the trial. I will conduct the trial as outlined herein and will complete the trial within the time designated.
I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of the trial. I will discuss this material with them to ensure that they are fully informed regarding the trial intervention and the conduct of the trial.

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Name of Institution (Printed)

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## SUMMARY

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<th>An Australian-lead, investigator-initiated, multi-centre, prospective, randomised, parallel group, double-blind, placebo-controlled trial to establish the effect(s) of routine administration of fluoxetine (20 mg once daily) in patients with recent stroke.</th>
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<tr>
<td>Short title</td>
<td>Assessment of fluoxetine in stroke recovery (AFFINITY) Trial</td>
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<tr>
<td>Acronym</td>
<td>AFFINITY</td>
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<td>Clinical phase</td>
<td>IIIb (i.e. fluoxetine is an established drug for depression, but not for stroke recovery; hence, possible new indication)</td>
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| Chief investigators | Dr Maree Hackett, The George Institute for Global Health  
Professor Graeme Hankey, Royal Perth Hospital & University of Western Australia |
| Primary Question | Does routine administration of fluoxetine (20mg od) in the 6 months after acute stroke improve patients’ functional outcome? |
| Trial design | Randomised, double blind placebo-controlled trial |
| Setting | Australian stroke units and hospitals |
| Eligibility criteria | Men or women aged 18 years or more with:  
- Clinical diagnosis of stroke 2-15 days previously (Day of stroke onset = Day 0, randomise on Day 2-15)  
- Brain imaging consistent with ischaemic or haemorrhagic stroke (including normal CT brain scan)  
- Persisting measurable focal neurological deficits (e.g. motor, somatosensory, visual, language, cognitive) present at randomisation and severe enough to warrant treatment from the perspective of patient or carer(s)  
Patients will be excluded if:  
- history of epileptic seizures  
- history of bipolar disorder  
- history of drug overdose or attempted suicide  
- allergy or contra indication to fluoxetine including:  
  - hepatic impairment (serum alanine aminotransferase [ALT] >120 U/l),  
  - renal impairment (creatinine > 180 micromol/l or eGFR < 50),  
  - Hyponatremia (sodium < 130mmol/L treat, repeat test and reassess for randomisation,  
  - current or recent (<1 month) depression requiring treatment with an SSRI antidepressant  
  - patient is taking medications with potential for serious interaction with Fluoxetine  
    - use of a monoamine oxidase inhibitor (MAOI) in last 5 weeks  
    - current treatment with Pimozide  
    - current treatment with other antidepressants (including St John’s Wort), unless patient agrees to discontinue use  
    - current treatment with tramadol, unless patient agrees to discontinue use  
    - current treatment with a neuroleptic drug |
- subarachnoid haemorrhage (except if secondary to intracerebral haemorrhage)
- unlikely to be available for follow up for the next 12 months e.g. no fixed home address
- life-threatening illness (e.g. advanced cancer) other than stroke likely to reduce 12 month survival
- pregnant, breast-feeding or of child-bearing age and not taking contraception (a minimum contraceptive measure is an oral contraceptive)
- enrolled in another interventional clinical research trial

**Randomisation**
Centralised via a web based randomisation system utilising a minimisation algorithm to achieve balance across the following four prognostic factors:

- Time from stroke onset (2-8 vs 9-15 days)
- Presence of a motor deficit
- Presence of aphasia
- Predicted probability of survival free of dependency at 6 months (0-15% vs 16-100%).

**Interventions**
- fluoxetine 20mg once daily or
- matching placebo

Duration: 6 months

- For patients unable to swallow: Trial medication delivered via enteral tube

**Outcome measures**
- Primary outcome at 6 months: simplified modified Rankin scale questionnaire (smRsq).
- Secondary outcomes at 6 and 12 months
  - Adherence to trial medication
  - New diagnosis of depression
  - Survival
  - Depression (Patient Health Questionnaire-9 item)
  - Cognition (Telephone Interview of Cognitive Status)
  - Communication (Stroke Impact Scale)
  - Motor function (SIS)
  - Fatigue (Vitality subscale of SF36)
  - Overall Health Status (SIS)
  - Health-related Quality of Life (EQ-5D-5L)
  - Health care utilisation
  - Simplified modified Rankin scale at 12 months

**Follow up**
- 1 and 3 months: Assessment of adherence, safety and mood.
- 6 and 12 months: Assessment of all outcome measures.

**Sample size estimate**
90% power to detect an absolute increase in the proportion of patients with an smRsq of 0-2 at 6 months from 50% to 57.5%

**Number of participants**
1,580 (790 in each group)

**Statistical methods**
Based on an ordinal analysis of smRsq adjusted for baseline variables included in minimisation algorithm

**Trial duration**
2011-2016
Figure 1. Flow summary of trial participants and assessments

1,580 patients

Informed consent, trial specific screen and baseline assessment

Central randomisation 2 to 15 days post-stroke

**Intervention** group (n=790)  **Control** group (n=790)

1 month on-intervention assessment

3 month on-intervention assessment and dispensing

End of 6-month intervention assessment

6-month off-intervention (12 month) assessment
List of abbreviations

AE  Adverse event
AR  Adverse reaction
CI  Confidence interval
CNS Central nervous system
CRF Case report form
DMC Data monitoring committee
GCP Good clinical practice
HREC Health review ethics committee
HRQoL Health related quality of life
ICH International conference on harmonisation
IMP Investigational medicinal product
IRB Institutional review board
ISF Investigator site file
MAOI Monoamine oxidase inhibitors
smRSQ Simplified modified Rankin scale questionnaire
OD Once daily
OR Odds ratio
PI Principal investigator at local centre
PPP Pharmaceutical packaging professionals
QALY Quality adjusted life year
SAE Serious adverse event
SAR Serious adverse reaction
SSRI Selective serotonin reuptake inhibitor
SUSAR Suspected unexpected serious adverse reaction
UAR Unexpected adverse reaction
1. BACKGROUND

Approximately 60,000 people have a stroke each year in Australia, of whom about 48,000 survive the first year. While close to 90% of stroke survivors live at home, at least half will have long-term residual disability [1,2]. This places a substantial burden on health and social services, informal carers, and the stroke survivors. Although more can be done to implement effective acute treatments, such as thrombolysis and organised multidisciplinary care in stroke units, there is a dearth of effective, safe, affordable and accessible interventions to facilitate recovery after stroke and increase functional independence after stroke. One promising intervention that needs to be tested is a widely used antidepressant medication, fluoxetine, a selective serotonin reuptake inhibitor (SSRI).

Animal studies indicate that SSRIs may be of benefit to stroke survivors

Animal models have produced results consistent with the hypothesis that fluoxetine, and possibly other SSRIs, might improve the clinical outcome of stroke survivors in a number of ways. First, brain stem and spinal cord α-motor neurons receive dense serotonergic inputs [3]. Serotonergic fibres also innervate secondary motor structures such as the basal ganglia [4]. Secondly, neuronal injury and loss are inevitable following stroke. It has long been established that neural regeneration can occur in the adult brain despite earlier beliefs that this was not possible [5]. SSRIs have a neurotrophic effect and stimulate neurogenesis in the adult brain [6,7]. SSRIs also stimulate the secretion of growth factors and other proteins associated with increased plasticity such as brain-derived neurotrophic factor (BDNF) [8,9] and phosphorylated cAMP response element binding (pCREB) protein [10]. Importantly, cell proliferation and the number of newborn neurons derived from the adult subgranular zone of the dentate gyrus in the hippocampus increases after prolonged treatment with fluoxetine [11]. Lastly, fluoxetine may have a neuroprotective role associated with its anti-inflammatory effect [12], thereby leading to a reduction of infarct size and enhancement of the expression of proteins (e.g. hypoxia-inducible factor 1 alpha) that facilitate recovery from ischaemic injury [13].

Human studies indicate that fluoxetine use may improve stroke recovery

Functional magnetic resonance imaging (fMRI) studies have found that a single dose of fluoxetine can modulate motor activity in healthy subjects [14]. A subsequent double-blind placebo-controlled crossover trial reported that a single dose of fluoxetine improved motor performance and increased fMRI activation in 8 patients who had a lacunar stroke resulting in a pure motor hemiparesis [15]. These findings were replicated in a more recent trial of 10 stroke patients [16]; participants who took a single dose of fluoxetine 20 mg showed increased muscle activation in the paretic arm. Other studies have produced similarly encouraging results. Dam and colleagues studied 52 post-stroke hemiplegic participants who were receiving physiotherapy [17]. Participants were randomly assigned to fluoxetine 20 mg daily, maprotiline 150 mg daily or placebo for 3 months. The fluoxetine group showed the greatest functional improvement as judged by a graded neurological scale and a measure of activities of daily living (Barthel Index [18]). In a smaller randomised trial enrolling unilateral stroke patients, the daily administration of 10 mg of the SSRI
Citalopram for 4 months was associated with less neurological impairment (National Institute of Health Stroke Scale score of 2.3 versus 3.5, p=0.03) at trial completion [19]. Mikami and colleagues conducted a randomized trial of fluoxetine (n=32) or nortriptyline (n=22) compared with placebo (n=29) [20]. After adjusting for age, depression, stroke severity, and rehabilitation intensity, 3 months of treatment with either nortriptyline or fluoxetine produced greater improvements in the modified Rankin Scale (mRs) measured at 1 year (i.e., 9 months after the start of treatment) compared with placebo. They also observed that the beneficial effects of treatment, as measured by smRsq scores compared with placebo, continued significantly for at least 1 year.

A recent systematic review identified six randomised controlled trials (RCTs) published before Dec 2009 which together recruited only 385 patients [21]. Meta-analysis demonstrated that fluoxetine use is associated with better neurological function (weighted mean difference, WMD = -4.72, 95% confidence interval (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 (Odds Ratio [OR] = 0.25, 95% CI 0.11 to 0.56). Two concerns about this meta-analysis however are that three of the studies did not have a placebo control arm and the studies included showed marked clinical and statistical heterogeneity.

The fluoxetine on Motor Rehabilitation after Ischemic Stroke’ (FLAME) trial

The fluoxetine on Motor Rehabilitation After Ischemic Stroke (FLAME) trial [22] is the largest trial to date to evaluate the effects of fluoxetine on motor recovery after stroke. 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 Myer motor score from baseline was greater among the 57 patients assigned fluoxetine (adjusted mean of +34.0 [95% CI 29.7 to 38.4]) than among the 56 patients assigned placebo (adjusted mean of +24.3 [95%CI 19.9 to 28.7]; p=0.003). The proportion of independent patients (mRs score 0-2) was also higher among patients assigned fluoxetine (26.3% fluoxetine vs. 8.9% placebo; p=0.015; OR = 3.8, 95% CI 1.2 to 10.7), although there were no significant differences at other cut-off points in the mRs.

While these results are promising, their internal validity may be compromised by random error (chance) due to the small number of patients and outcomes. Their external validity (generalisability) may also be compromised by the recruitment of only three to four patients per year on average from each of the participating centres. The promising but inconclusive results, of the FLAME trial have invigorated interest in the use of fluoxetine after stroke and precipitated calls for a conclusive trial [23].

2. OBJECTIVES

Hypothesis

Participants with acute stroke who are randomly assigned to early treatment with fluoxetine compared to placebo will experience an improved rate and range of recovery of their functional neurological deficits, as shown by a shift to better categories of the simplified modified Rankin questionnaire (smRsq) [24,25] and a
larger proportion of participants being independent (determined by a score of 0-2 on the smRsq [24,25]) at 6 months after stroke.

Primary Objective
To determine if the routine administration of fluoxetine (20mg once daily) for 6 months started at 2-15 days post onset of acute stroke improves participants’ functional outcome at 6 months after stroke.

Secondary Objectives
To determine if, at 6 and 12 months post randomisation, the routine administration of fluoxetine (20mg od) in the 6 months after an acute stroke:

1. Improves participant:
   - Adherence to trial medication
   - Survival
   - Mood (PHQ-9) [26]
   - Cognitive function (TICSm) [27]
   - Communication (SIS) [28]
   - Motor function (SIS) [28]
   - Overall health status (SIS) [28]
   - Health-Related Quality of Life (EQ-5D-5L) [29]

2. Reduces participant:
   - New diagnosis of depression requiring treatment with antidepressants
   - Fatigue (vitality domain of the SF-36) [37]

3. Is safe and does not cause serious adverse events, such as
   - Hyponatraemia, Epileptic Seizures, Bleeding, and Cardiovascular events.

4. Has persisting benefits on functional outcome (smRsq), mood, cognition, HRQoL and fatigue 6 months after treatment is discontinued (i.e. 12 months after randomisation).

5. Reduces the cost of health and social care over the first year.

6. Is cost-effective.

3. TRIAL PLAN and PROCEDURES

Setting
Participants will be recruited from stroke units, rehabilitation facilities and clinics across Australia, between late 2011 and 2015, and followed-up until mid 2016.

Trial design
Randomised, parallel group, double-blind, placebo-controlled clinical trial.

Trial population

Inclusion criteria
All the following criteria:

- Men or women aged 18 years or over
- Clinical diagnosis of stroke 2-15 days previously (Day of stroke onset = Day 0, randomise on Day 2-15)
• Brain imaging consistent with ischaemic or haemorrhagic stroke (including normal CT brain scan)
• Persisting measurable focal neurological deficits (e.g. motor, somatosensory, visual, language, cognitive) present at randomisation and severe enough to warrant treatment from the perspective of patient or carer(s).

Exclusion criteria
Any of the following criteria:
• history of epileptic seizures
• history of bipolar disorder
• history of drug overdose or attempted suicide
• allergy or contra indication to fluoxetine including
  ➢ hepatic impairment (serum alanine aminotransferase [ALT] >120 U/l),
  ➢ renal impairment (creatinine > 180 micromol/l or eGFR < 50),
  ➢ Hyponatremia (sodium < 130 mmol/L): treat, repeat test and reassess for randomisation
• current or recent (<1 month) depression requiring treatment with an SSRI antidepressant
• patient is taking medications with potential for serious interaction with Fluoxetine
  o use of a monoamine oxidase inhibitor in last 5 weeks
  o current treatment with Pimozide
  o current treatment with other antidepressants (including St John’s Wort), unless patient agrees to discontinue use
  o current treatment with tramadol, unless patient agrees to discontinue use
  o current treatment with a neuroleptic drug;
• subarachnoid haemorrhage (except if secondary to intracerebral haemorrhage)
• unlikely to be available for follow up for the next 12 months e.g. no fixed home address
• life-threatening illness (e.g. advanced cancer) other than stroke likely to reduce 12 month survival
• pregnant, breast-feeding or of child-bearing age and not taking contraception (a minimum contraceptive measure is an oral contraceptive)
• enrolled in another interventional clinical research trial

Co-enrolment
Co-enrolment is permissible in studies that could not possibly confound the results of AFFINITY, by having an influence on any of the outcomes in AFFINITY. Purely observational studies are therefore acceptable but inclusion in another trial in which a patient is assigned to an intervention that could influence their outcome in the first 12 months after stroke in another randomised controlled trial automatically excludes the patient from participating in AFFINITY.
Consent

All participants must be fully informed, understand, and consent by one of the approved methods outlined in section 6 of this protocol (see below) to participate in the trial for its duration of 12 months.

Primary responsibility for the appropriate consenting of participants will lie with the Principal Investigator at each site.

Randomisation

Consenting participants who meet the inclusion and exclusion criteria will be randomised 2 to 15 days after stroke onset by means of a computerised central randomisation service (www.affinitytrial.org) – address to be confirmed) that is available 24 hours a day.

After entering the baseline demographic and clinical data of the participant randomisation will be conducted using a minimisation algorithm to achieve balance between the two treatment groups for the following four prognostic factors:

1. Delay between stroke onset (2-8 vs 9-15 days. To ensure balanced since if severity was balanced but this was not the prognosis would be potentially quite different given the wide time window. Spontaneous recovery is much quicker within the first week than later;
2. Presence of a motor deficit. To ensure equal in both groups to ensure subgroup is balanced;
3. Presence of aphasia. To ensure equal in both groups to ensure subgroup is balanced.
4. Probability of survival free of dependency at 6 months (0-0.15 vs 0.16-1.0) [1]. To ensure that at baseline patients have equal probability of being alive and independent (smRSq: 0-2);

The purpose of the minimisation process is to ensure an equitable prevalence or balance of major prognostic factors for survival free of dependency between the two treatment arms. At the time of randomisation, the following six prognostic variables will be collected: age, living alone, independence in activities of daily living before the stroke, the verbal component of the GCS, arm power, and ability to walk [1]. The trial web site will have installed a computer program that can automatically calculate the probability of survival free of dependency at 6 months, based on the prediction model developed and validated by Counsell et al [1]. It is anticipated that about half of randomised patients with have a predicted probability of 0-15%, and the other half 16 to 100% of being independent at 6 months. At randomization, the patients will be assigned to the group which minimises the difference across all four variables but only with a probability of 0.8 (rather than 1.0). This adds a random element to the treatment assignment which means that the likely treatment allocation cannot be guessed in advance.

The randomisation system will automatically generate a treatment allocation in a ratio of 1:1 active drug (fluoxetine) or placebo and an email/fax to the centre coordinator and the local research pharmacist to ensure that the allocated treatment is prescribed.
**Intervention**

Participants will be randomly assigned to six months treatment with either:

- Fluoxetine, 20mg capsules, to be taken once daily,

or

- Placebo capsules that match the fluoxetine capsules once daily.

If the patient is unable to swallow the medication will be delivered via enteral tube by opening the capsule and administering the contents.

The fluoxetine capsules will be a General Health Brand of capsule purchased from the Royal Adelaide Hospital by Pharmaceutical packaging professionals (PPP) in South Australia.

The placebo capsules will be manufactured by PPP.

The placebo capsules will match the fluoxetine capsules in appearance (same colour and shape), weight and texture.

The capsules will be placed in bottles at PPP.

Each bottle will contain 110 capsules of either fluoxetine or matching placebo.

Each bottle will serve as a 3 month (90 day) supply of trial medication (there are 20 extra capsules per bottle to allow for delays in follow-up appointments or lost trial medication).

The bottles will be labelled by PPP in accordance with the randomisation schedule, according to regulatory requirements, and stored at PPP in accordance with standards of the South Australian Department of Human Services in a cGMP dedicated warehouse at below 25 degrees celsius.

The bottles will be dispensed by PPP directly to the Pharmacy departments of the trial centres, with two bottles per participant (i.e. each bottle containing 3 monthly supplies of 110 capsules per bottle). Participating centres will instruct their hospital pharmacies to store the product under appropriate conditions below 25 degrees celsius.

Investigators will prescribe the trial medication by means of a local hospital prescription. The prescription will be for a 3 month supply of 110 capsules of AFFINITY trial medication, fluoxetine or placebo, to be taken once daily as best fits with the participant’s daily routine, with or without food. It is the responsibility of each principal investigator to ensure that accurate records of trial medication prescriptions are maintained.

After receiving a local hospital prescription for the trial drug, the medication will be dispensed to the participant by the local hospital pharmacy. Dispensing will occur at baseline and the 3-month assessment. It is the responsibility of each trial pharmacy to ensure that accurate records of trial medication dispensing and returns are maintained.
**Medications to avoid**

Medications to avoid are those with serotonergic activity, including non-antidepressant medications such as

- Tramadol
- Other synthetic opiates, and
- St John’s Wort and Pimozide
- MAOIs including those for Parkinson’s disease.

Anti-coagulant effects of medications such as heparin and warfarin may be enhanced by concomitant administration of fluoxetine, and therefore requires careful monitoring.

**Drugs Metabolised by P4502D6 (CYP2D6):** Approximately 3% to 10% of the normal population has a genetic defect that leads to reduced levels of activity of cytochrome P4502D6 (CYP2D6). Such individuals have been referred to as poor metabolisers of drugs such as dextromethorphan and tricyclic antidepressants. Many drugs, such as most antidepressants including fluoxetine and other selective uptake inhibitors of serotonin, are metabolised by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolisers.

Fluoxetine, like other agents that are metabolised by P4502D6 (CYP2D6), inhibits the activity of this isoenzyme and thus may make normal metabolisers resemble poor metabolisers. Therapy with medications that are predominantly metabolised by P4502D6 (CYP2D6) and that have a relatively narrow therapeutic index (eg flecainide, carbamazepine and tricyclic antidepressants) should be initiated at the low end of the dose range if a patient is taking fluoxetine concurrently or has taken it in the previous 5 weeks.

**Potential Effects of Co-administration of Drugs Highly Bound to Plasma Proteins:** Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (e.g. warfarin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs.

**Tryptophan:** Five patients receiving fluoxetine hydrochloride in combination with tryptophan experienced adverse reactions, including agitation, restlessness and gastrointestinal distress.

**Warfarin:** Altered anticoagulant effects (laboratory values and/or clinical signs and symptoms), with no consistent pattern, but including increased bleeding, have been reported uncommonly when fluoxetine is co-administered with warfarin. As is prudent in the concomitant use of warfarin with many other drugs, patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.
**CNS Active Drugs:** The risk of using Fluoxetine generichealth in combination with other CNS active drugs has not been systematically evaluated. Data have been derived from circumstances which do not directly reflect the clinical setting. The clinical significance of *in vitro* and individual case report data is unknown. Nonetheless, caution is advised if the concomitant administration of Fluoxetine generichealth and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status.

**Anticonvulsants:** Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

**Antipsychotics:** Some evidence suggests a possible pharmacodynamic and/or pharmacokinetic interaction between some serotonin specific reuptake inhibitors (SSRIs) and some antipsychotics, including possible elevation of blood levels of haloperidol and clozapine. Clinical studies of pimozide with other antidepressants demonstrate an increase in drug interaction or QTc prolongation. While a specific study with pimozide and fluoxetine has not been conducted, the potential for drug interactions or QTc prolongation warrants restricting the concurrent use of pimozide and fluoxetine.

**Benzodiazepines:** The half-life of concurrently administered diazepam may be prolonged in some patients and coadministration of alprazolam may result in increased plasma alprazolam concentrations.

**Lithium:** There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

**Serotonergic drugs:** Co-administration with serotonergic drugs (e.g. SNRIs, SSRIs, tramadol or triptans such as sumatriptan) may result in serotonin syndrome.

**Monoamine Oxidase Inhibitors:** The combined administration of fluoxetine and a monoamine oxidase inhibitor (MAOI) has been associated with the development of serotonin syndrome, a serious, sometimes fatal, reaction in patients receiving an SSRI in combination with a MAOI and in patients treated with fluoxetine and a MAOI in close temporal proximity. Some cases presented with features resembling neuroleptic malignant syndrome. Symptoms and signs of serotonin syndrome include: clonus, myoclonus, tremor, shivering, hyperreflexia, hyperthermia, rigidity, autonomic instability with possible rapid fluctuations of vital signs and mental status changes that include extreme agitation progressing to delirium and coma.

**Other Antidepressants:** In two studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2 to 10-fold when fluoxetine has been administered in combination. This influence may persist for three weeks or longer after fluoxetine is discontinued. Thus, the dose of tricyclic antidepressant (TCA) may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued.
St John’s Wort: In common with other SSRIs, pharmacodynamic interactions between fluoxetine and the herbal remedy St John’s Wort (Hypericum perforatum) may occur, which may result in an increase of undesirable effects [38].

Participant diary of adherence and compliance
Participants will be asked to keep a trial diary that will enable them to record the use of trial and other medication (e.g. concurrent/additional antidepressant medication) and any possible adverse effects.
Participants will be encouraged to adhere to (i.e. continue) the allocated treatment and will be asked to record the date, reason and duration of any temporary or permanent discontinuation.
Participants will also be encouraged to comply with (i.e. consistently take) the allocated trial medication and will be asked to bring their capsule bottles with them to their follow-up visits so that the compliance rate (the ratio of taken doses to total possible doses) can be calculated.

Emergency Unblinding
Unblinding is strongly discouraged.
In the event of an emergency, such as a suspected serotonin syndrome, discontinue the trial medication, and treat the patient in the usual manner. The trial medication must be discontinued after emergency unblinding.
If access to the database is really required, to determine the treatment allocation for the participant, PPP has supplied unblinding envelopes that will be held in hospital pharmacies or in secure storage with trial medication. PPP will also hold a central list for unblinding purposes and provide 24 hours a day phone contact for unblinding when necessary.

Overdose
Symptoms of overdose of fluoxetine include nausea, vomiting, and seizures. Cardiovascular dysfunction, ranging from asymptomatic arrhythmias to cardiac arrest, can occur, as may pulmonary dysfunction, and CNS dysfunction, ranging from excitation to coma.
Cardiac and vital sign monitoring is recommended, along with general symptomatic and supportive measures.
No specific antidote is known. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage. Forced diuresis, dialysis, haemoperfusion, and exchange transfusion are unlikely to be of benefit.
In managing over dosage, consider the possibility of multiple drug involvement. An extended time for close medical observation may be needed in participants who
have taken excessive quantities of a tricyclic antidepressant if they are also taking, or have recently taken, fluoxetine.

Fatalities attributed to overdose of fluoxetine alone are extremely rare; the severity is usually mild and course benign.

**Premature termination of trial medication**

Participants may choose to stop taking the allocated treatment – in which case they will be followed up as per protocol and included in the primary analyses. The reason for stopping the treatment prematurely will be recorded in the participants case report form (CRF). If withdrawal results from a SAE or Suspected Unexpected Serious Adverse Reaction (SUSAR) the event will be reported as per protocol (see below).

Participants may also choose to withdraw completely from the trial, so that no further data will be collected on that participant. If the participant is willing we will record the reason for any such withdrawal.

**Stopping the trial medication at 6 months (or earlier)**

Sudden cessation of an SSRI may lead to a withdrawal syndrome characterised by symptoms including anxiety, restlessness, insomnia, headache and tremor). However, of all the SSRIs, fluoxetine has the longest half-life (4-6 days) and therefore a withdrawal syndrome is very uncommon and tapering of the dose (especially from only 20mg od) is not regarded as necessary.

**Return of any remaining trial medication at the end of the trial**

Upon trial completion participants will be asked to return the trial medication to the randomising centre. The coordinating centre will track supplies of the trial medication, at the end of the trial it will ensure the destruction of all returned dispensed trial medication.

### 4. TRIAL ASSESSMENTS, MEASUREMENTS, ENDPOINTS and ADVERSE EVENTS

**Baseline assessment**

Consent, screening, and all assessments will be conducted in person by site staff using standardised computer-assisted forms and standardised procedures, protocols following interview training. A schedule of assessments is shown below in Table 1.

All participants will be interviewed at baseline (between 2 and 15 days post stroke), and the following will be recorded: age, sex, date of stroke, marital status, living arrangements, employment status, independence in activities of daily living before stroke; medical history: co-morbidity, previous and/or current depression, medication use; post stroke information: Oxfordshire Community Stroke Project (OCS [30]) classification (total anterior circulation, TACS; partial anterior circulation, PACS; lacunar, LACS; posterior circulation, POCs); The National Institutes of Health Stroke Scale or (NIHSS) a scale of neurological impairments developed by the National Institutes of Health that is used to gauge the severity of a stroke; Simplified
Modified Rankin Scale (smRsq) a measure of functional ability; and the cause of stroke. Participants will also be asked to keep a trial diary to record the use of trial and other medication.

It will be recorded whether the baseline and follow-up information is obtained directly from the participants or from appropriate informants (e.g., spouse, children).

28 and 90 days
At 28 days +/- 7 days and at 90 days +/- 14 days, the participant will undergo a face-to-face interview with site staff to assess survival, primary outcome (smRsq), adherence to medication, recent depression, current mood (PHQ-9), living arrangements, adverse events, current medications, and to dispense trial medication (90 day visit only).

180 and 365 days
At 180 days +/- 14 days and at 365 days +/- 14 days the participant will undergo a face-to-face interview with site staff to assess survival, primary outcome (smRsq), adherence to medication, recent depression, current mood (PHQ-9), cognition (TICSm), fatigue (vitality subscale of SF36), health care utilisation, health-related quality of life (EQ-5D-5L), living arrangements, adverse events, current medications.
If participant is unable to attend a face-to-face interview a telephone interview can be conducted.
If any of the baseline or follow-up assessment tools are unavailable alternative assessments will be used.

Laboratory Tests
A pregnancy test will be performed on those patients of child-bearing age at baseline to confirm eligibility to the trial.
Liver function tests will be performed at baseline, the 28 day follow-up assessment and the 90 day follow-up assessment. If the ALT enzyme is 3 or more times above the upper limit of normal (>120 U/l), it should be reassessed after one week, and if high levels persist the trial medication not be started, or if started, should be discontinued.

Serum creatinine and eGFR will be measured at baseline, the 28 day follow-up assessment and the 90 day follow-up assessment. If the serum creatinine is > 180 micromol/ l or eGFR < 50 the test will be repeated after one week.

Laboratory tests completed within 15 days post stroke onset will be accepted as baseline measures.

Urea and electrolytes will be measured at baseline, the 28 day follow-up assessment and the 90 day follow-up assessment. If the urea result is > 8.0mmol/L the test will be repeated in one week. If the blood sodium concentration is low (< 130 mmol/L), the cause should be ascertained (by checking plasma and urine sodium and
osmolality) and, if due to syndrome of inappropriate ADH section, the recommended treatment is fluid restriction to 800ml-1 litre per day, and to repeat the test after one week.

**Table 1. Trial assessment schedule**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent*</td>
<td>X*</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In/exclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Details of Stroke</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological Impairments (NIHSS)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classification of stroke - OCSP [30]</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cause of Stroke</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>PHQ-9 [26]</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Medical comorbidities</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Medications in use</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Compliance monitoring</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUSARS/SAEs</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cognition - TICSm [27]</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Overall Health Status - SIS [28]</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Health-related Quality of Life - EQ-SD-5L [29]</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fatigue (Vitality subscale of SF36) [37]</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Health care utilization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>ALT</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine and eGFR</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Urea and electrolytes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Informed Consent can also be obtained before the baseline visit, then an appointment could be made to come back for a baseline visit.

**Outcome Measures**

**Primary**

**Functional recovery**

The primary endpoint (outcome measure) is the degree of disability or dependence in daily activities at 6 months after randomisation, as measured by the smRsq [24,25]
and analysed using ordinal logistic regression to maximise power and to avoid any problems of including participants with a smRsq score \( \leq 2 \) immediately after their stroke [32-34].

The smRsq is derived from the following five questions:

1. Could you live alone without any help from another person? This means being able to bathe, use the toilet, shop, prepare or get meals, and manage finances.
2. Can you do everything that you were doing right before your stroke, even if slower and not as much?
3. Can you walk (from one room to another) without help from another person?
4. Are you completely back to the way you were right before your stroke?
5. Are you bedridden or needing constant supervision?

The smRsq is scored as follows:

0  no symptoms;
1  no significant disability despite symptoms, able to carry out all usual duties and activities;
2  slight disability, unable to carry out all previous activities but able to look after own affairs without assistance;
3  moderate disability requiring some help, but able to walk without assistance;
4  moderate-severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance;
5  severe disability, bedridden incontinent, and requiring constant nursing care and attention;
6  dead.

The smRsq is simple, time efficient, reliable, widely used and accepted and can be completed by proxies.

The smRsq will be measured at baseline, 28 days, 90 days, 180 days and 365 days. If there are patients in whom face-to-face assessment of smRSq is impractical, we will engage, as a second step, a postal smRSq with telephone follow-up for non-responders.

*Secondary*

**Adherence to medication**

Adherence will be measured:

a) Subjectively, by response to the question ‘On average, since the last follow up how many times per week was the trial medication taken? ‘0’, ‘1-2’, 3-4’, ‘5-6’ or ‘7’ times per week (acknowledging that unintentional non-adherence is likely
to be underestimated because some patients are unaware of their forgetfulness); and

b) Objectively, by pill counts and collection of returned trial bottles (acknowledging that absence of tablets in the bottle does not necessarily mean adherence to taking the tablets).

Information on participants who temporarily or permanently stop trial medication, and dates of and reasons for stopping will be recorded. Analysis of medication adherence will compare groups based on the reported non-adherence and number of residual tablets.

Depression
Participants will be asked if they have been diagnosed with depression since their last assessment.

The PHQ-9 [26] is a 9 item depression scale which scores each of the 9 DSM-IV [35] criteria as ‘0’ (not at all) to ‘3’ (nearly every day) generating a total score from 0-27.

<table>
<thead>
<tr>
<th>Patient health questionnaire (PHQ-9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Question 1</strong></td>
</tr>
<tr>
<td>Over the past two weeks how often have you been bothered by any of the following problems?</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1 Little interest or pleasure in doing things</td>
</tr>
<tr>
<td>2 Feeling down, depressed, or hopeless</td>
</tr>
<tr>
<td>3 Trouble falling/staying asleep, sleeping too much</td>
</tr>
<tr>
<td>4 Feeling tired or having little energy</td>
</tr>
<tr>
<td>5 Poor appetite or overeating</td>
</tr>
<tr>
<td>6 Feeling bad about yourself or that you are a failure or have let yourself or family down</td>
</tr>
<tr>
<td>7 Trouble concentrating on things, such as reading the newspaper or watching television</td>
</tr>
<tr>
<td>8 Moving or speaking so slowly that other people could have noticed. Or the opposite: being so fidgety or restless that you have been moving around more than usual</td>
</tr>
<tr>
<td>9 Thoughts that you would be better off dead or of hurting yourself in some way</td>
</tr>
</tbody>
</table>

Add the individual scores together to get a total score. Of those patients who score 10 or more in primary care, most (7.6% of all patients in primary care) will have a score 10 to 14, which indicates either subthreshold depression or moderate depression [35]; a smaller proportion (3.4% of all patients in primary care) will have a score of 15 to 19, indicating moderate to severe depression; and the smallest proportion (2% of all patients in primary care) will have a score of ≥20.

**Question 2**
If you indicated any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with people?

<table>
<thead>
<tr>
<th>Not difficult at all</th>
<th>Very difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somewhat difficult</td>
<td>Extremely difficult</td>
</tr>
</tbody>
</table>

Further information and copies of the PHQ-9 in various languages are available at www.phqscreeners.com/ and www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/
Scores of $\geq 15$ indicate the presence of clinically significant depressive symptoms that require treatment. It has been validated for use with stroke survivors and can generate a DSM-IV [35] equivalent diagnosis.

The PHQ-9 will be administered at baseline (covering the four weeks before stroke), 1, 3, 6 and 12 months.

**Cognition**

The TICSm [27] has been validated for assessment of cognitive function for research purposes and in stroke. Scores are normally distributed and are sensitive to change over time.

The 13-item TICSm includes orientation, recent and delayed memory, attention and comprehension assessments with a maximum possible score of 39.

The TICSm can be administered via the telephone or be used to assess people with visual difficulties or poor hand-eye coordination.

**Fatigue**

The vitality subscale of the full SF-36 will be used to assess participants’ level of fatigue. [37]

**Overall Health Status**

The Stroke Impact Scale (SIS) [28] will provide an overall assessment of participant outcome and will allow us to assess the effect of treatment on specific outcomes of importance to participants.

The SIS is a comprehensive, health status measure that was developed with input from participants and caregivers. It includes 8 domains (strength, hand function, ADL/IADL, mobility, communication, emotion, memory and thinking, participation) from across the full impairment-participation continuum. It also provides an overall assessment of recovery and has been evaluated successfully for use by proxy respondents [36].

**HRQoL**

HRQoL will be measured by means of the EQ-5D-5L [29]. The EQ-5D is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.
Health care utilisation
At the 6 and 12 month assessment participants will provide information on health care service usage.
Data linkage will also be used to collect information on hospital admissions, General Practitioner/Specialist visits and medical services. This will require an application to Medicare and a separate consent form.

Adverse reactions and events
AFFINITY is evaluating fluoxetine, a very widely used SSRI that has been licensed for the treatment of depression since 1988 and used in thousands of patients with stroke to treat depression and emotionalism. Even though there is the potential for interactions of fluoxetine with medications frequently prescribed for stroke patients, such as aspirin and warfarin, these rarely cause significant problems. The trial materials given to the participant, and/or their carer will contain details of the known adverse reactions to fluoxetine [39,40].

Adverse effects of newer antidepressants and suggested management

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Comment</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>Occurs in about one in 10 people who take second generation antidepressants but is less common with fluoxetine</td>
<td>Check blood pressure standing and lying; symptoms may improve over time; decrease dose or change treatment. Ensure adequate fluid intake</td>
</tr>
<tr>
<td>Sedation</td>
<td>Not common but can occur</td>
<td>Sedation may be desirable; it may improve over time. Change time of dosing and treatment</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Probably dose related</td>
<td>Tolerance may develop; change treatment; suggest sugarless gum or saliva substitutes</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Common but often not asked about</td>
<td>Consider reducing dose, waiting for the effects to improve, switching to a different antidepressant, or consider sildenafil</td>
</tr>
<tr>
<td>Insomnia</td>
<td>Common problem but hard to distinguish from insomnia caused by depression</td>
<td>Change time of dosing (earlier or later may help), pay attention to sleep hygiene, try a different antidepressant, or possibly try short course of benzodiazepine, zopiclone, or low dose trazadone</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>Antidepressants may paradoxically increase suicidal thoughts in those aged under 30</td>
<td>Review often (within a week of starting antidepressants and continue until no longer clinically needed). No evidence exists that asking about suicide makes people more likely to harm themselves. Prescribe small amounts of medication.</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Often occurs when starting SSRIs</td>
<td>Consider using a benzodiazepine for no longer than two weeks</td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>Particularly a problem in the elderly and more common with SSRIs</td>
<td>Check sodium before and after starting treatment, and consider changing to mirtazapine if it becomes problematic</td>
</tr>
<tr>
<td>Serotonin syndrome</td>
<td>Characterised by changes in mental state (eg confusion or agitation), autonomic instability (eg high temperature, shivering, sweating, changes in blood pressure), and neuromuscular hyperactivity (eg clonus or hyper-reflexia). Seen particularly with SSRIs and other drugs that effect serotonin</td>
<td>Stop the antidepressant. Use supportive measures such as hydration, management of hyperthermia, and benzodiazepines. Consider cyproheptadine or chlorpromazine in severe cases</td>
</tr>
<tr>
<td>Discontinuation syndrome</td>
<td>More common with SSRIs that have a short half life (eg paroxetine or venlafaxine)</td>
<td>Decrease dose over four weeks. Warn the patient</td>
</tr>
</tbody>
</table>
SSRIs = selective serotonin reuptake inhibitors.


A population-based cohort study of more than 60,000 patients aged 65 years or more who were diagnosed with depression and followed up found that 764,650 prescriptions for SSRI antidepressants were issued and that, compared with when these drugs were not being used, SSRIs were associated with significantly higher rates of:

- all cause mortality (11.42% per year if taking fluoxetine vs 7.04% per year if not taking antidepressant; adjusted hazard ratio [HR]: 1.54, 95% confidence interval [CI]: 1.48 to 1.59),
- stroke/transient ischaemic attack (2.57% per year fluoxetine vs 2.23% per year no antidepressant; HR: 1.17, 1.10 to 1.26),
- myocardial infarction (1.31% vs 1.0% per year; HR: 1.15, 1.04 to 1.27),
- upper gastrointestinal bleeding (0.48% vs 0.42% per year; HR: 1.22, 1.07 to 1.40),
- falls (5.6% vs 3.5% per year; HR: 1.66, 1.58 to 1.73),
- fracture (2.76% vs 1.76% per year; HR: 1.58, 1.48 to 1.68),
- epilepsy/seizures (0.31% vs 0.21% per year; HR: 1.83, 1.49 to 2.26),
- attempted suicide/self harm (0.53% vs 0.25% per year; 2.16, 1.71 to 2.71), and
- hyponatraemia (0.49% vs 0.29% per year; HR: 1.52, 1.33 to 1.75) [39].

Rates of most outcomes were highest in the first 28 days after starting an antidepressant, and also in the first 28 days after stopping.

The main concern with the above results is that they are based on observational studies and are therefore prone to residual confounding and indication bias [39]. Indication bias occurs when patients are prescribed drugs for a condition that is itself associated with the outcome of interest. This means that apparent associations with fluoxetine may be due to the condition for which it was prescribed (i.e. depression) rather than to the drug itself. Nevertheless, the above data are presented to indicate what could be causal adverse effects [39].

Irrespective of whether fluoxetine treatment is administered or not, about 20% of hospitalized patients with stroke would be expected to die in the first month after a stroke and another 10% by the end of the first year as part of the natural history of stroke. Up to a third will develop a chest or urinary infection whilst in hospital, up to 5% may develop venous thromboembolism, epileptic seizures or gastrointestinal bleeding.

**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 AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or considered related to the medicinal product. 

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 drug reaction (UAR) is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator brochure for an unapproved investigational product or package insert/summary of product characteristic for an approved product). 

The product information will be provided which can be used as a guide to determine whether the event is expected or unexpected. 

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 hospitalisation or prolongation of existing hospitalisation; 
- results in persistent or significant disability or incapacity; 
- results in a congenital anomaly or birth defect. 

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided: 

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning as defined in the bullet points above. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. 

A hospitalization is to be considered an SAE only if it is an official admission. In addition, a hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE. 

Recording and Reporting 

All SAEs, SARs and SUSARs will be recorded from the time that the trial participant signs the informed consent form until the end of the follow-up. SARs will also be assessed at 1, 3, 6 and 12 month assessments. 

Any SAE, SAR and SUSAR, regardless of adherence to the protocol, treatment or a causal relationship between the treatment and reaction, must be reported to the coordinating centre immediately (within 24 hours after the investigator becomes aware of the SAE/SAR/SUSAR). This can be done using the Serious Adverse
Event/Reaction page on the web-based CRF, or when not available, via fax or via a free phone number which will allow the participants or their doctors to either leave a message (if non urgent) or to access a Trial Doctor (if urgent).

All SAEs will be recorded on source documents.

All SUSARs will be reported to the TGA in an expedited manner (immediately and in no case later than 15 calendar days from notification of sponsor personnel) and all SAEs will be reported to ethics committees at three month intervals. The Data Monitoring Committee (DMC) will closely monitor the relative frequency of SAEs in the treatment and control groups and, in turn, will advise the steering committee of any concerns.

Where applicable, the PI may be required to submit a follow up report to provide further information so that the outcome of the SAE can be recorded.

All follow up to the original SAE or recurrent episodes, must be reported, as detailed above, within 24 hours of receipt by the investigator by faxing a completed SAE form, or completing the form online.

The PI is responsible for reporting the SAE to the Ethics Committee according to local guidelines.

**Pregnancy**
A separate form will be used to report pregnancies during the trial.

**Monitoring Side Effects and Interactions of fluoxetine**
Participants will be seen at one month after baseline to monitor for drug safety and adverse effects. Any reported unacceptable adverse effects will be discussed with one of the trial clinicians and the participant’s GP. This will be used to guide a decision regarding their ongoing participation in the trial. In addition, we will provide all participants and their GPs with a list of common adverse effects and drug interactions.

We will also arrange for a routine test of urea and electrolytes at 1 month to monitor for hyponatremia that may sometimes occur in those taking an SSRI due to the syndrome of inappropriate antidiuretic hormone (SIADH). If the blood sodium concentration is low, and the cause is SIADH, the recommended treatment is fluid restriction to 800ml-1 litre per day, and repeat the blood sodium test in 3-7 days, by which time the sodium concentration should have returned to normal. There should be no need to stop the trial medication.

GPs will be able to contact a trial clinician if any medication concerns arise during the trial.

**Development of a Major Depressive Episode**
Depression is a not infrequent consequence of stroke, occurring in around a third of stroke survivors. It is therefore likely that a number of participants will develop depression during the trial period and this would include those taking the active
medication. It is envisioned that these depressive illnesses will be detected in one of two ways:

1) During one of the trial visits as either a score of 15 or greater on the PHQ-9 indicating a major depressive illness of moderate or severe severity or

2) Diagnosed during a visit to their general practitioner or another clinician e.g. physician

We will contact the GPs of all enrolled participants by mail at the commencement of enrolment in the trial to provide information about the trial and to inform them about the trial medication their patient is potentially taking. Participants without regular GPs will be encouraged to nominate one. In this letter we will make the GP aware of potential side effects and drug interactions of fluoxetine. Participants will receive similar information and be asked to make any clinician they may see aware that they are potentially taking fluoxetine as part of a clinical trial. We will alert the GP in the event that during the course of the trial the participant displays moderate/severe depressive symptoms (PHQ-9 score > 15). It is envisaged that GPs will manage their patients as per their usual practice however we will include some suggestions about how they may want to manage their patient in the advent of them developing a major depressive illness during the trial. These suggestions will be:

1) Consider non-pharmacological treatments such as advising an increase in social outlets, regular exercise or referral to a clinical psychologist. Clinical psychology can be accessed through the Medicare Better Access initiative and is available free of charge to Australian residents and citizens. There is provision for up to 12 sessions per year as part of a GP mental health treatment plan (http://www.health.gov.au/internet/main/publishing.nsf/Content/mental-ba-over).

2) If the GP feels that additional antidepressant medication is necessary, consider adding 10 mg of fluoxetine to the participant’s trial medications and increasing this further to 20 mg after 4-6 weeks if ineffective. This would mean that some participants would potentially be on 40 mg of fluoxetine a day. This dose has been shown to be effective and safe. Combination therapy (using two or more antidepressants simultaneously) should best be avoided in view of the risk of serotonergic syndrome, especially if using another SSRI. GPs would be advised to use a non-serotonergic antidepressant such as reboxetine or one with less serotonergic activity such as mirtazapine if they chose to initiate combination therapy.

3) Consider referral to a specialist psychiatrist.

In addition contact details will be provided for the two trial psychiatrists (Professor Osvaldo P Almeida and Associate Professor Andrew H Ford) who will be available for advice.
Identify patient with stroke

Check eligibility

Consent

Collect Baseline data

Randomise

Fluoxetine 20mg for 6/12 Placebo for 6/12 Letter informing GP

28 +/- 7 days: face-to-face assessment on treatment
Survival, primary outcome (smRsq), medical compliance, depression, mood (PHQ-9), living arrangements, adverse events, current medications, blood test for sodium, renal function and liver function.

90 +/- 14 days face-to-face assessment on treatment
Survival, primary outcome (smRsq), medical compliance, depression, mood (PHQ-9), living arrangements, adverse events, current medications

180 +/- 14 days: face-to-face assessment at end of treatment
Survival, primary outcome (smRsq), medical compliance, depression, mood (PHQ-9), cognition (TICS), Fatigue (vitality subscale of SF36), health care utilisation, overall health status (SIS), health-related quality of life (SF-12), living arrangements, adverse events, current medications

365 +/- 14 days face-to-face assessment at end of follow-up off treatment
Survival, primary outcome (smRsq), medical compliance, depression, mood (PHQ-9), cognition (TICS), Fatigue (vitality subscale of SF36), health care utilisation, overall health status (SIS), health-related quality of life (SF-12), living arrangements, adverse events, current medications

Patient flagged with national statistics for death certificate
5. STATISTICAL METHODS

Primary analysis
The primary analysis will compare the treatment groups’ smRsq scores at the six month follow-up using an ordinal analysis adjusted for any baseline imbalance in those factors included in our minimisation algorithm and will retain participants in their original assigned treatment groups. Ordinal analysis (also known as shift analysis) on smRsq scores will be used to determine change (improvement) in outcome distribution over the full range of smRsq outcomes. Shift analysis has several distinct advantages over dichotomised outcome analysis including: benefits and harm seen at all disease state transitions contribute to the outcome; making the least assumptions about the type of participants in the trial and increasing trial power [34].

In the ordinal analysis will use the following subgroups: Age (<70, ≥ 70yrs), ischaemic vs. haemorrhagic stroke and OCSP classification (TACS, PACS, LACS, POCS) [30].

Secondary analyses
The smRsq scores at the twelve month follow-up of the two treatment groups will be compared using an ordinal analysis and a categorical analysis of smRsq 0-2 vs. 3-6 to establish if any benefits for the primary outcome at 6 months are maintained.

The two treatment groups will be compared with respect to the following secondary outcomes at 6 and 12 months and change from baseline:

- adherence to trial medication;
- mood (PHQ-9);
- survival (Cox proportional hazards model);
- cognition (TICS-m);
- fatigue (vitality subscale of the SF-36);
- HRQoL (EQ-5D-5L);
- communication and overall impact of stroke (SIS, and for each of 9 domains);
- new diagnosis of depression requiring treatment with antidepressants;
- adverse reactions.

A trial-based economic evaluation will be conducted from the perspective of the health sector and will assess the incremental cost per Quality Adjusted Life Year (QALY) of the intervention strategy over placebo. In estimating costs, inpatient costs (e.g. investigations, interventions, medicines, and adverse events) and outpatient costs (investigations, interventions, medicines, rehabilitation, equipment, home modifications, community services, informal care, loss of employment, ambulance...
transfers, and hospital readmission) will be estimated from each follow-up. These will be costed using standard published rates (e.g. from MBS for non-hospital medical services, PBS for prescribed medications and AR-DRG cost weights for hospital services). The average costs incurred by participants in both treatment groups during the trial will be assessed.

Quality of life will be derived from EQ-5D-5L scores [29]. The EQ-5D is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

Descriptive statistics
For descriptive purposes baseline characteristics will be presented by treatment groups. Discrete variables will be summarised by frequencies and percentages, continuous variables by use of standard measures of central tendency and dispersion, mean and standard deviation (SD) or median and interquartile range (IQR). All variables will be graphically analysed (i.e. box plots) to determine if variances between groups are equal and variables with unequal variances will be transformed (e.g. log transformation) where necessary to ensure that any difference in coefficients are true differences.

Sample size
The AFFINITY trial will recruit 1580 participants over 4 years. Based on data from the CLOTS trial [41] and the SCAST [42] trials, we expect the proportion of participants not dependent on others (as indicated by a score of 0-2 on the smRsq [24]) to be 50% in the AFFINITY control group at six months (see Table 2).

**Table 2. Expected distributions of smRsq scores at 6 months**

<table>
<thead>
<tr>
<th>smRsq score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>0.10</td>
<td>0.20</td>
<td>0.20</td>
<td>0.15</td>
<td>0.10</td>
<td>0.10</td>
<td>0.15</td>
</tr>
<tr>
<td>Intervention group</td>
<td>0.13</td>
<td>0.24</td>
<td>0.21</td>
<td>0.14</td>
<td>0.09</td>
<td>0.08</td>
<td>0.12</td>
</tr>
</tbody>
</table>

We expect that random assignment to fluoxetine will increase odds of being functionally independent (smRsq 0-2) at 6 months by 1.35 compared with control, which is a conservative estimate based on the effect of fluoxetine detected in the FLAME trial (OR = 3.8, 95% CI 1.2 to 10.7) [22]. An odds ratio of 1.35 is equivalent to an increase in the proportion of participants being functionally independent at 6 months by 7.5 percentage points (absolute increase; i.e. from 50% to 57.5%) providing a clinically significant relative improvement of 15% (relative increase).

Assuming a common odds ratio of 1.35 in the ordinal logistic regression [32] and 90% power, the trial will require 1580 participants taking into account the fact that up to 10% of living participants may be lost to follow-up.
With an effective sample size of 1420 participants, we will also be able to detect a mean difference in the PHQ-9 score of 1 with more than 90 percent power. This is based on a standard deviation of 5 as reported in other trials [43, 44].

The target of 1580 will be reviewed by the blinded steering committee taking account accruing data on the distribution of participants (across both treatment groups) between different smRsq categories and losses to follow up since these may influence the power of the trial. The steering committee would have the option of increasing the target for randomisation to maintain the trial power.

6. ETHICS
Declaration of Helsinki
The trial will be performed in agreement with the Declaration of Helsinki and in accordance with relevant national and international regulatory and ethical frameworks.

Ethics review and approval
All participating hospital sites will receive approval from their relevant ethics committee or institutional review board before initiation.

It is the responsibility of the principal investigator (PI) at each participating center to obtain written approval from the relevant ethics committee and regulatory bodies before starting the trial.

Written informed consent will be obtained from each participant or their legal surrogate if the participant is unable to provide it.

Participant information and informed consent
The Investigator will be responsible for ensuring informed consent is obtained from the participant or, if not fully competent, from a proxy (next of kin, responsible family member or legal surrogate according to local requirements) before any protocol specific procedures are carried out.

The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants will receive adequate oral and written information about the trial – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or designated person, and cover all the elements specified in the Participant Information Sheet/Informed Consent Form(s).

Participants will be asked to consent to participation in the trial, to take the allocated medication, and to be followed-up over the 12 months of the trial. They will also be asked if they agree to optional follow-up beyond 12 months to 5 years after randomization.
Participants will also be informed that, at any time, they can withdraw their consent to participate in the trial without loss of benefits to which they otherwise would be entitled, and this is documented in the participant information sheet.

The participant will be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant will be given sufficient time to consider the information provided.

The participant will be informed and agree to their medical records being inspected by regulatory authorities.

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original copy of the informed consent form will be kept in the patient’s medical records. The participant or person who the legal surrogate who has provided the informed consent will receive a copy of this document and a copy filed in the Investigator Site File (ISF).

The consent procedures for this trial are listed below and should be followed according to local IRB guidelines which may differ between States and Territories in Australia.

**Participant Consent**
Wherever possible, the alert and conscious participant will be approached directly to give written informed consent. An information statement will be given to the participant and the implications for consenting to the trial will be explained by a clinician familiar with the trial protocol.

**Person Responsible Consent (proxy, next of kin or surrogate) – non WA sites**
If the patient is not fully competent to give informed consent, for example because of a reduced level of consciousness or confusion, the patient’s ‘person responsible’ will be approached to provide informed consent on his or her behalf, if approved by the local ethics committee.

Under the Guardianship Act 1987 a ‘person responsible’ is the legally appointed guardian, their spouse or de-facto spouse or same sex partner, or if there is none, their unpaid carer, or if there is none, their relative or friend who has a close relationship with the person.

The rules and definitions of for the terms ‘next of kin’, ‘person responsible’ and ‘legal surrogate’ in the context of a clinical trial may differ between States and Territories in Australia, therefore the specific wording should be checked in each region and local ethics approval is required before enrolling patients in the trial.

The patient will be made aware of this process as soon as they are well enough and have an opportunity to withdraw the consent. If a patient regains legal capacity and the ability to give informed consent and is willing to continue participation in the trial, the patient will be asked to sign their own consent form. This informed consent should be obtained in addition to the next of kin or legal surrogate consent.

If the patient is dying or is still unable to record their personal consent by the time of completed follow up on the trial, the consent given by their person responsible will
stand and trial data will be retained. The reason for not obtaining the participant’s consent will be documented, dated and signed in the participant’s file.

If a participant is discharged from hospital before it has been possible to gain personal consent, the PI will make attempts to inform the participant during follow up of the trial and gain written consent. If this has been unsuccessful after a minimum of 3 documented occasions, the consent given by their person responsible will stand and the trial data will be retained. The reason for not obtaining the participant’s consent will be documented, dated and signed in the participant’s file.

In the case of a participant’s death, the PI should use discretion on a case by case basis before contacting the ‘person responsible’ in recognition of the potential distress that may exist as the result of a death. In either case, an explanation of the lack of patient consent will be document in the participant’s file.

**Withdrawal of Consent**
The information statement provided to the participant and/or the next of kin or surrogate will clearly state that the participant can be withdrawn or be withdrawn from the trial at any time without prejudice and explanation. Such withdrawal should be documented in the participant’s file.

**Data protection and retention**
All trial documentation will be kept for a minimum of 15 years following trial closure in a secure environment, according to regulatory and ethical requirements.

**Insurance and Indemnity**
Sites participating in the trial will seek insurance or indemnity to cover their liability from their local institution. If sites are unable to provide insurance alternative options will be investigated.

7. **QUALITY ASSURANCE**

**Source documents**

The purpose of source documents is to document the existence of the participant and substantiate the integrity of the trial data collected. The investigator must maintain source documents for each participant in the trial. Source documents include original documents related to the trial, to medical treatment and the history of the participant. They can be hospital or clinic medical records, laboratory data and results of any other test or assessments.

Original case report form may be kept at individual hospital sites. Original consent forms may also be kept at hospital sites, with a copy sent to the coordinating office in Perth.
Monitoring of participating centres

Prior to the initiation of the trial at any participating centre, all designated research staff including the PI, Co-Investigator(s) and Research Nurse(s) will be trained in the methods of the trial and a trial monitor, a representative of the trial coordinating centre, will visit each participating centre to confirm there are adequate facilities and medical resources to conduct the trial. Before initiation of the trial, the PI and Co-investigators will sign and provide up-to-date Curriculum Vitaes (CVs) to the coordinating centre.

During the trial, representatives of the coordinating centre will perform site visits and communication by telephone, mail and e-mail will be used as needed to supplement site visits. The purpose of these visits will be to ensure that the trial is conducted according to the protocol, ICH-GCP guidelines and meets relevant regional regulatory requirements. A report of each visit will be prepared by the monitor and reviewed by the coordinating centre.

In summary, the specific aims of the visits will be to:

a. Confirm existence of each randomised participant
b. Confirm written informed consent is obtained from each participant
c. Confirm adherence to the protocol including consistency with inclusion and exclusion criteria
d. The completeness and accuracy of the case record forms (CRFs) and source documentation.
e. Compliance with regulations.

Adequate and accurate source documents allow the investigator and the site monitor to verify the reliability and authenticity of data recorded on the electronic CRFs and ultimately to validate that the clinical trial was carried out in accordance with the protocol. Essential documents must be retained until notified in writing by the coordinating centre.

The trial monitor may also monitor the trial pharmacies to ensure that trial medication supply records are in order and there are sufficient supplies available, that the medication supply is stored under appropriate conditions and are not being used beyond expiry dates and that the handling of returned and/or unused trial medication supplies complies with trial procedures.

At completion of the trial, the monitor will confirm with the site that there are plans in place for the long-term storage of all the relevant data and source documentation (for 15 years).

Protocol deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved trial that is not consistent with the current protocol or consent document. A protocol deviation may be an omission, addition or change in any procedure described in the protocol
Except for changes to eliminate an immediate hazard to participants, the approved protocol will be followed as specified. Any significant protocol deviation will be documented on a protocol violation form and sent to the central trial management centre as soon as possible. A copy will also be stored in the participant’s case record folder.

Protocol amendments
Any significant change in the trial protocol will require an amendment. Once the steering committee has approved a protocol amendment, it is the responsibility of the principal investigator to submit this to each HREC for written approval. The approval letter, signed by the HREC chair, must refer specifically to the investigator, the protocol number, the protocol title, the protocol amendment number, and the date of the protocol amendment. The protocol amendment may be implemented only after it has been approved by the HREC. A protocol change intended to eliminate an apparent immediate hazard to participants may be implemented immediately, but the change must then be documented in an amendment, reported to the HREC and the trial coordinating centre within 5 working days.

If the revision is an administrative change (such as the addition or removal of committee members), a letter explaining the change(s) along with a copy of the amended pages(s) of the protocol must be submitted to the HREC for their information. No formal approval from the HREC is required prior to implementation of administrative changes.

Responsibilities of the principal investigator (PI) at each participating centre.
It is the responsibility of the principal investigator (PI) at each participating centre to

- obtain written approval from the relevant ethics committee and regulatory bodies before starting the trial;
- ensure informed consent is obtained from the participant (or proxy) before any protocol specific procedures are carried out;
- ensure participants are managed in according with good clinical practice
- report any protocol amendments and SAEs to the local hospital ethics committee and to the trial coordinating centre

Change of investigators
If during or after the conduct of the trial, any investigator withdraws from conducting the trial, retires or relocates the responsibility for maintaining records may be transferred to another investigator, the coordinating centre or HREC. The coordinating centre must agree and be notified of any planned change and all associated documentation must be updated.

Auditing by regulatory bodies
The trial may be audited by inspectors appointed by government regulatory authorities. CRFs, source documents and other trial files must be accessible at all trial
sites at times of monitoring and auditing during the course of the trial and after the completion of the trial.

**Termination of the trial**

**Termination by the Steering Committee**
The trial management or Steering committee may terminate the entire trial or terminate the trial at a particular centre at any time for any of the following reasons:
- Failure to enrol participants
- Protocol violations
- Inaccurate or incomplete data
- Unsafe or unethical practices
- Questionable safety of the treatment
- Suspected lack of efficacy of the treatment
- Lack of treatment safety
- Administrative decision

**Termination by the Investigator**
If the investigator terminates the trial prematurely, the investigator will do the following:
- Return all trial materials to the coordinating centre
- Provide the HREC and the coordinating centre a written statement describing why the trial was terminated prematurely

The discontinuations of therapy will be reviewed by the steering committee.

**Notification of Trial Closure**
In addition to interim reports as required by the HREC, the principal investigator will complete a final report notifying each HREC of the conclusion of the clinical trial. The final report sent to the HREC is also sent to the coordinating centre.

8. **FUNDING**
The start-up phase of the trial is being supported by funds from National Health and Medical Research Council Program Grant (Application ID: 1013612).

9. **TRIAL ORGANISATION**
AFFINITY is co-ordinated jointly by independent investigators at The George Institute for Global Health in Sydney and the Royal Perth Hospital and University of Western Australia in Perth, Australia.

Dr Maree Hackett (George Institute) and Prof Graeme Hankey (Royal Perth Hospital & University of Western Australia) are co-principal investigators and will share oversight and direction of the trial. A trial steering committee consisting of the grant holders will undertake the academic oversight of the trial.

Day to day trial co-ordination will be managed centrally at Royal Perth Hospital by a trial management group headed by Prof Graeme Hankey.
The independent DMC will oversee the safety of participants in the trial.

**Steering Committee**
Dr Maree Hackett, The George Institute for Global Health (co-chair)
Clinical Professor Graeme J. Hankey, Royal Perth Hospital & University of Western Australia (co-chair)
Professor Osvaldo Almeida, University of Western Australia
Professor Craig S. Anderson, The George Institute for Global Health
Associate Professor Christopher Beer, University of Western Australia
Mr Laurent Billot, The George Institute for Global Health
Professor Martin S. Dennis, The University of Edinburgh
Professor Leon Flicker, Royal Perth Hospital
Associate Professor Andrew Ford, University of Western Australia
Associate Professor Stephen Jan, The George Institute for Global Health
Dr Gillian Mead, The University of Edinburgh

The Steering Committee carries the responsibility for the trial. Tasks include:
- Approval of the trial protocol and any amendments.
- Prevention, recognition and resolution of problems that may interfere with the conduct of the trial.
- Classification of outcome events on which no consensus is reached by the Auditing Committee.
- Deciding whether or not the trial should continue, based on the recommendations of the DMC.
- Writing manuscripts.

**Data monitoring committee**
An independent DMC will be established to oversee the safety of participants in the trial. During the period of recruitment, interim analyses of baseline and follow up data will be supplied, in strict confidence, to the chairperson of the DMC, along with any other analyses that the committee may request. In the light of these analyses, the DMC will advise the chairperson 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 trial 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 trial (or seek extra data). Unless this happens however, the steering committee, the collaborators and central administrative staff will remain ignorant of the interim results.
Tasks include:

- Analyses of unblinded interim data.
- Unblinded analysis of adverse events.
- Formulation of recommendations to the steering committee on the continuation of the trial.
- Offering unsolicited recommendations to the steering committee, for example after publication of results of a similar trial.

10. UNITED KINGDOM (UK) FOCUS TRIAL

The AFFINITY investigators are collaborating with colleagues at the Department of Geriatric Medicine, Edinburgh and the Neurosciences Trial Unit in Edinburgh, United Kingdom who are concurrently planning a similar trial (Fluoxetine or Control Under Supervision, FOCUS), with similar eligibility criteria, treatments, outcome measures and follow-up schedule.

AFFINITY and FOCUS will have a joint DMC. Providing access to the confidential reports of the both trials will enable the DMC to make recommendations to the trial steering groups based on all available evidence, whether the trials should continue to recruit unchanged, should continue to recruit only in certain subgroups, or should stop recruiting.

AFFINITY and FOCUS investigators plan to conduct a prospective meta-analysis which will enable us to identify smaller, but clinically important effect sizes, which neither trial could identify individually, and also allow us to identify clinically worthwhile effects in pre-specified subgroups. The investigators have registered the review title with the Cochrane Stroke Group. AFFINITY and FOCUS investigators will also share the work or costs involved in maintaining up to date systematic reviews of the evidence. The advantages of carrying out two closely related but independent trials, rather than a single international trial are:

- Trial methods can match resources, infrastructure and regulations available in that country.
- Governmental funding agencies will only be asked to fund research activity in their country.
- Avoids the complexities of moving drug and placebo, and of dealing with indemnity, across international boundaries.
- That each trial will test the effect of fluoxetine in their particular environment e.g. with the intensity of therapy available in that country, with the background use of SSRIs etc to ensure that the result applies to patients in that country.
- That the health economic analyses will be tailored to that country so that the implication for their health and social services can be deduced.
- The Australian investigators will be able to explore secondary outcomes which will assist in elucidating possible mechanisms for any effects found.
- There will be greater local ownership of the project and therefore hopefully improved recruitment and retention.
- Concordant trial results that are statistically significantly positive would provide really reliable data that would be applicable to potentially millions of future patients a year.
11. TRIAL TIMETABLE

Start up phase
A start up phase, which aims to randomise 200 patients in the first year, will establish whether our protocol is feasible. This 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 realistic 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 adherence rate, and reasons for non adherence, which will influence our predicted effect size and power calculations.
3. the follow-up rate.

Assuming that the start-up phase does not identify the need to substantially redesign the trial we would plan to move seamlessly from the start-up phase to the main phase of the trial, without stopping recruitment or performing any analyses to determine treatment effects.

Table 3. TIMELINES AND MILESTONES

<table>
<thead>
<tr>
<th>Date</th>
<th>Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feb-Jun 2011</td>
<td>Protocol and case report form design</td>
</tr>
<tr>
<td>May 2011</td>
<td>Source drug supply and matching placebo &amp; packaging</td>
</tr>
<tr>
<td>November 2011</td>
<td>Apply to ethics committees</td>
</tr>
<tr>
<td>November 2011</td>
<td>Database design commences</td>
</tr>
<tr>
<td>August 2012</td>
<td>Start up recruiting sites</td>
</tr>
<tr>
<td>Sep 2012</td>
<td>First participant in trial</td>
</tr>
<tr>
<td>March 2013</td>
<td>Six month assessment of first participant in trial</td>
</tr>
<tr>
<td>Sep 2013</td>
<td>Twelve month assessment of first participant in trial</td>
</tr>
<tr>
<td>Aug 2015</td>
<td>Completion of recruitment of 1580 participants</td>
</tr>
<tr>
<td>Sep 2016</td>
<td>Completion of last twelve month assessment</td>
</tr>
<tr>
<td>Nov 2016</td>
<td>Finalisation of database and data lock</td>
</tr>
<tr>
<td>Dec 2016</td>
<td>Presentation and publication of main results</td>
</tr>
</tbody>
</table>

Main phase
The main trial will recruit a total of 1580 patients in order to have sufficient statistical power to detect differences in a primary outcome of smRsq score for the entire group, and to detect differences in specific outcomes in pre-specified strata based on neurological deficits at baseline.
As it may not be feasible to enrol sufficient participants to reliably detect moderate effect sizes in these strata on our primary outcome (mRS) 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 strata.

2. To work collaboratively with a parallel trial (FOCUS) based in the UK, which has a similar design to increase the overall sample size and the numbers of participants in each of the important strata. We will perform pre-specified meta-analyses to maximise our chances of detecting benefits in specific strata.

12. **PUBLICATION OF TRIAL RESULTS**
Ownership of the data arising from this trial resides with the trial team. 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.
REFERENCES


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6. Schmidt HD, Duman RS. The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. Behav Pharmacol. 2007;18:391-418


APPENDICES

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### APPENDIX 1: NATIONAL INSTITUTE OF HEALTH STROKE SCORE

<table>
<thead>
<tr>
<th>National Institute of Health Stroke Score (NIHSS):</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1a. Level of Consciousness</strong></td>
<td></td>
</tr>
<tr>
<td>0: Alert</td>
<td></td>
</tr>
<tr>
<td>1: Not alert, but arousable with minimal stimulation</td>
<td></td>
</tr>
<tr>
<td>2: Not alert, requires repeated stimulation to attend</td>
<td></td>
</tr>
<tr>
<td>3: Coma (makes at least only reflex movements to pain)</td>
<td></td>
</tr>
<tr>
<td><strong>1b. LOC questions</strong> (ask patient the month &amp; her/his age)</td>
<td></td>
</tr>
<tr>
<td>0: Answers both correctly</td>
<td></td>
</tr>
<tr>
<td>1: Answers one correctly (score 1 if patients speech affected other by than aphasia)</td>
<td></td>
</tr>
<tr>
<td>2: Both incorrect</td>
<td></td>
</tr>
<tr>
<td><strong>1c. LOC commands</strong> (ask patient to open/close eyes &amp; form/release a fist)</td>
<td></td>
</tr>
<tr>
<td>0: Obey both correctly</td>
<td></td>
</tr>
<tr>
<td>1: Obey one correctly</td>
<td></td>
</tr>
<tr>
<td>2: Both incorrect</td>
<td></td>
</tr>
<tr>
<td><strong>2. Best gaze</strong> (only horizontal eye movements)</td>
<td></td>
</tr>
<tr>
<td>0: Normal</td>
<td></td>
</tr>
<tr>
<td>1: Partial gaze palsy (can be overcome) or single nerve palsy (III, IV or VI)</td>
<td></td>
</tr>
<tr>
<td>2: Total gaze paresis or Forced deviation (cannot be overcome with rapid head turn)</td>
<td></td>
</tr>
<tr>
<td><strong>3. Visual field testing</strong></td>
<td></td>
</tr>
<tr>
<td>0: No visual field loss</td>
<td></td>
</tr>
<tr>
<td>1: Partial hemianopia (including quadrantanopia or visual extinction (see 11))</td>
<td></td>
</tr>
<tr>
<td>2: Complete hemianopia</td>
<td></td>
</tr>
<tr>
<td>3: Bilateral hemianopia (including bilateral blindness from any cause)</td>
<td></td>
</tr>
<tr>
<td><strong>4. Facial Paresis</strong> (ask patient to show teeth/raise eyebrows &amp; close eyes tightly)</td>
<td></td>
</tr>
<tr>
<td>0: Normal symmetrical movement</td>
<td></td>
</tr>
<tr>
<td>1: Minor paralysis (flattened nasolabial fold, asymmetry on smiling)</td>
<td></td>
</tr>
<tr>
<td>2: Partial paralysis (total or near total paralysis of lower face)</td>
<td></td>
</tr>
<tr>
<td>3: Complete paralysis of one or both sides (absence of facial movement in the upper &amp; lower face)</td>
<td></td>
</tr>
<tr>
<td><strong>5. Motor function – Arm</strong></td>
<td></td>
</tr>
<tr>
<td>0: Normal (extends arms 90° (or 45°) position for 5 seconds without drift)</td>
<td></td>
</tr>
<tr>
<td>1: Drift</td>
<td></td>
</tr>
<tr>
<td>2: Some effort against gravity</td>
<td></td>
</tr>
<tr>
<td>3: No effort against gravity</td>
<td></td>
</tr>
<tr>
<td>4: No movement</td>
<td></td>
</tr>
<tr>
<td>U: Untestable (joint fused or limb amputated) (do not add score)</td>
<td></td>
</tr>
<tr>
<td><strong>5. Motor function – Leg</strong></td>
<td></td>
</tr>
<tr>
<td>0: Normal (holds leg in 30° position for 5 seconds without drift)</td>
<td></td>
</tr>
<tr>
<td>1: Drift</td>
<td></td>
</tr>
<tr>
<td>2: Some effort against gravity</td>
<td></td>
</tr>
<tr>
<td>3: No effort against gravity</td>
<td></td>
</tr>
<tr>
<td>4: No movement</td>
<td></td>
</tr>
<tr>
<td>U: Untestable (joint fused or limb amputated) (do not add score)</td>
<td></td>
</tr>
<tr>
<td><strong>7. Limb ataxia</strong> (finger/nose, heel/shin testing)</td>
<td></td>
</tr>
<tr>
<td>0: No ataxia</td>
<td></td>
</tr>
<tr>
<td>1: Present in one limb</td>
<td></td>
</tr>
<tr>
<td>2: Present in two limbs</td>
<td></td>
</tr>
<tr>
<td>U: Untestable (joint fused or limb amputated) (do not add score)</td>
<td></td>
</tr>
<tr>
<td><strong>8. Sensory</strong> (use pinprick to test arms, legs, trunk &amp; face – compare the sides)</td>
<td></td>
</tr>
<tr>
<td>0: Normal</td>
<td></td>
</tr>
<tr>
<td>1: Mild to moderate decrease in sensation</td>
<td></td>
</tr>
<tr>
<td>2: Severe or total sensory loss (including those in coma)</td>
<td></td>
</tr>
<tr>
<td><strong>9. Best Language</strong> (ask patient to describe picture, name items, read sentences)</td>
<td></td>
</tr>
<tr>
<td>0: No aphasia</td>
<td></td>
</tr>
<tr>
<td>1: Mild to moderate aphasia</td>
<td></td>
</tr>
<tr>
<td>2: Severe aphasia</td>
<td></td>
</tr>
<tr>
<td>3: Mute (including those in coma)</td>
<td></td>
</tr>
<tr>
<td><strong>10. Dysarthria</strong> (ask patient to read several words)</td>
<td></td>
</tr>
<tr>
<td>0: Normal articulation</td>
<td></td>
</tr>
<tr>
<td>1: Mild to moderate slurring of words</td>
<td></td>
</tr>
<tr>
<td>2: Near unintelligible or unable to speak</td>
<td></td>
</tr>
<tr>
<td>U: Untestable (intubated or other physical barrier to speech) (do not add score)</td>
<td></td>
</tr>
<tr>
<td><strong>11. Extinction &amp; inattention</strong> (formerly neglect) (use visual or sensory double stimulation)</td>
<td></td>
</tr>
<tr>
<td>0: Normal</td>
<td></td>
</tr>
<tr>
<td>1: Inattention or extinction to bilateral stimulation in one of the sensory modalities</td>
<td></td>
</tr>
<tr>
<td>2: Severe hemi-inattention or hemi-inattention to more than one modality</td>
<td></td>
</tr>
</tbody>
</table>

**Total Score**
APPENDIX 2: NATIONAL INSTITUTE OF HEALTH STROKE SCORE
You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.
MAMA
TIP – TOP
FIfty – FIfty
THANKS
HUCKLEBERRY
BASEBALL PLAYER
APPENDIX 2: SIMPLIFIED MODIFIED RANKIN SCALE

Could you live alone without any help from another person? This means being able to bathe, use the toilet, shop, prepare or get meals, and manage finances.

Yes  No

Are you able to do everything that you were doing right before your stroke, even if slower and not as much?

Yes  No

Are you completely back to the way you were right before your stroke?

Yes  No

Are you able to walk without help from another person?

Yes  No

Are you bedridden or needing constant supervision?

No  Yes

0  1  2  3  4  5
APPENDIX 3: OXFORDSHIRE COMMUNITY STROKE PROJECT CLASSIFICATION OF CLINICAL STROKE SYNDROMES

The Oxfordshire Community Stroke Project classification of clinical stroke syndromes

Total anterior circulation syndromes
- hemiparesis and homonymous hemianopia contralateral to the brain lesion, and
- either dysphasia or visuospatial perceptual disturbance
- ± hemisensory deficit contralateral to the brain lesion.

Partial anterior circulation syndrome
- one or more of unilateral motor or sensory deficit, aphasia or visuospatial neglect (combined or not with homonymous hemianopia)
- motor or sensory deficit may be less extensive than in lacunar syndromes (for example, hand alone).

Lacunar syndrome
Any one of the following four syndromes involving at least two of the three areas (face, arm, leg), and involving the limb in its entirety:
- pure motor hemiparesis, or
- pure hemisensory deficit of one side of the body, or
- hemisensory-motor deficit, or
- ataxic hemiparesis (dysarthria clumsy hand syndrome or ipsilateral ataxia with crural hemiparesis)
- no visual field defect
- no new disturbance of higher cortical or brainstem function

Posterior circulation syndromes
Any one of:
- cranial nerve impairment
- unilateral or bilateral motor or sensory deficit
- disorder of conjugate eye movement
- cerebellar dysfunction
- homonymous hemianopia
- cortical blindness.
APPENDIX 4: PATIENT HEALTH QUESTIONNAIRE – 9 ITEM

INSTRUCTIONS FOR USE
for doctor or healthcare professional use only

PHQ-9 QUICK DEPRESSION ASSESSMENT

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment on accompanying tear-off pad.
2. If there are at least 4 √s in the blue highlighted section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.
3. Consider Major Depressive Disorder
   —if there are at least 5 √s in the blue highlighted section (one of which corresponds to Question #1 or #2)
   Consider Other Depressive Disorder
   —if there are 2 to 4 √s in the blue highlighted section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician and a definitive diagnosis made on clinical grounds, taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient. Diagnosis of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up √s by column. For every √: Several days = 1  More than half the days = 2  Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying PHQ-9 Scoring Card to interpret the TOTAL score.
5. Results may be included in patients’ files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

PHQ-9 SCORING CARD FOR SEVERITY DETERMINATION
for healthcare professional use only

Scoring—add up all checked boxes on PHQ-9
For every √: Not at all = 0; Several days = 1; More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Depression Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>None</td>
</tr>
<tr>
<td>5-9</td>
<td>Mild depression</td>
</tr>
<tr>
<td>10-14</td>
<td>Moderate depression</td>
</tr>
<tr>
<td>15-19</td>
<td>Moderately severe depression</td>
</tr>
<tr>
<td>20-27</td>
<td>Severe depression</td>
</tr>
</tbody>
</table>
APPENDIX 5: TELEPHONE INTERVIEW FOR COGNITIVE STATUS – M

APPENDIX

Telephone Interview for Cognitive Status (TICS-M)

Orientation
1. (i) What day of the week is it? Day
   (ii) What is today’s date? Date
   (iii) What season are we in? Month
       Year
2. What is your age? Season
3. What is your telephone number? (Code + number) Age:

Registration/Free Recall
4. I’m going to read you a list of 10 words.
   Please listen carefully and try to remember
   them. When I am done, tell me as many as
   you can in any order. Ready?

   Cabin
   Pipe
   Elephant
   Chest
   Silk
   Theatre
   Watch
   Whip
   Pillow
   Giant

   Now, tell me all the words you can remember

Attention/Calculation
5. Please take 7 away from 100
   Now continue to take 7 away from what
   you have left over until I ask you to stop.

   93
   86
   79
   72
   65

   6. Please count backwards from 20 to 1
   No mistakes

   7. What do people usually use to cut paper?
   Scissors
   Cactus
   E, QE, QE2
   Correct surname
   West

   8. What is the prickly green plant found in the desert?
   
   9. Who is the reigning monarch now?
   
   10. Who is the Prime Minister now?
   
   11. What is the opposite of east?

Comprehension, Semantic and Recent Memory

Language/Repetition

Delayed Recall
12. Please say this ‘Methodist Episcopal’

   13. Please repeat the list of 10 words I read earlier

   Cabin
   Pipe
   Elephant
   Chest
   Silk
   Theatre
   Watch
   Whip
   Pillow
   Giant

   maximum of 39

Score ‘1’ for each correct answer and ‘0’ if incorrect
APPENDIX 6: SF-36 (VITALITY SUBSCALE)

Q9a  The following questions are about how you feel and how things have been with you in the past four weeks. As I read each statement, please give me the one answer that comes closest to the way you have been feeling. How much of the time during the past four weeks did you feel full of life?

1...............................All of the time
2........................................Most of the time
3.......................................A good bit of the time
4........................................Some of the time
5...............................A little of the time
6.......................................None of the time

Q9e  And how much of the time during the past four weeks did you have a lot of energy?

1...............................All of the time
2........................................Most of the time
3.......................................A good bit of the time
4........................................Some of the time
5...............................A little of the time
6.......................................None of the time

Q9g  How much of the time during the past four weeks did you feel worn out?

1...............................All of the time
2........................................Most of the time
3.......................................A good bit of the time
4........................................Some of the time
5...............................A little of the time
6.......................................None of the time

Q9i  How much of the time during the past four weeks did you feel tired?

1...............................All of the time
2........................................Most of the time
3.......................................A good bit of the time
4........................................Some of the time
5...............................A little of the time
6.......................................None of the time
APPENDIX 7: STROKE IMPACT SCALE

Stroke Impact Scale
VERSION 3.0

The purpose of this questionnaire is to evaluate how stroke has impacted your health and life. We want to know from **YOUR POINT OF VIEW** how stroke has affected you. We will ask you questions about impairments and disabilities caused by your stroke, as well as how stroke has affected your quality of life. Finally, we will ask you to rate how much you think you have recovered from your stroke.
## Stroke Impact Scale

These questions are about the physical problems which may have occurred as a result of your stroke.

<table>
<thead>
<tr>
<th>1. In the past week, how would you rate the strength of your...</th>
<th>A lot of strength</th>
<th>Quite a bit of strength</th>
<th>Some strength</th>
<th>A little strength</th>
<th>No strength at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Arm that was most affected by your stroke?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Grip of your hand that was most affected by your stroke?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Leg that was most affected by your stroke?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Foot/ankle that was most affected by your stroke?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

These questions are about your memory and thinking.

<table>
<thead>
<tr>
<th>2. In the past week, how difficult was it for you to...</th>
<th>Not difficult at all</th>
<th>A little difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Remember things that people just told you?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Remember things that happened the day before?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Remember to do things (e.g. keep scheduled appointments or take medication)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Remember the day of the week?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Concentrate?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Think quickly?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. Solve everyday problems?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
These questions are about how you feel, about changes in your mood and about your ability to control your emotions since your stroke.

3. In the past week, how often did you...

<table>
<thead>
<tr>
<th></th>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Feel sad?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Feel that there is nobody you are close to?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Feel that you are a burden to others?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Feel that you have nothing to look forward to?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Blame yourself for mistakes that you made?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Enjoy things as much as ever?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. Feel quite nervous?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>h. Feel that life is worth living?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>i. Smile and laugh at least once a day?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

The following questions are about your ability to communicate with other people, as well as your ability to understand what you read and what you hear in a conversation.

4. In the past week, how difficult was it to...

<table>
<thead>
<tr>
<th></th>
<th>Not difficult at all</th>
<th>A little difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Say the name of someone who was in front of you?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Understand what was being said to you in a conversation?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Reply to questions?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Correctly name objects?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Participate in a conversation with a group of people?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Have a conversation on the telephone?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. Call another person on the telephone, including selecting the correct phone number and dialing?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
The following questions ask about activities you might do during a typical day.

<table>
<thead>
<tr>
<th></th>
<th>In the past 2 weeks, how difficult was it to...</th>
<th>Not difficult at all</th>
<th>A little difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Could not do at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>Cut your food with a knife and fork?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b.</td>
<td>Dress the top part of your body?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c.</td>
<td>Bathe yourself?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d.</td>
<td>Clip your toenails?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e.</td>
<td>Get to the toilet on time?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f.</td>
<td>Control your bladder (not have an accident)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g.</td>
<td>Control your bowels (not have an accident)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>h.</td>
<td>Do light household tasks/chores (e.g. dust, make a bed, take out garbage, do the dishes)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>i.</td>
<td>Go shopping?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>j.</td>
<td>Do heavy household chores (e.g. vacuum, laundry or yard work)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

The following questions are about your ability to be mobile, at home and in the community.

<table>
<thead>
<tr>
<th></th>
<th>In the past 2 weeks, how difficult was it to...</th>
<th>Not difficult at all</th>
<th>A little difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Could not do at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>Stay sitting without losing your balance?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b.</td>
<td>Stay standing without losing your balance?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c.</td>
<td>Walk without losing your balance?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d.</td>
<td>Move from a bed to a chair?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e.</td>
<td>Walk one block?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f.</td>
<td>Walk fast?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g.</td>
<td>Climb one flight of stairs?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>h.</td>
<td>Climb several flights of stairs?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>i.</td>
<td>Get in and out of a car?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
The following questions are about your ability to use your hand that was MOST AFFECTED by your stroke.

<table>
<thead>
<tr>
<th>7. In the past 2 weeks, how difficult was it to use your hand that was most affected by your stroke to...</th>
<th>Not difficult at all</th>
<th>A little difficult</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Could not do at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Carry heavy objects (e.g. bag of groceries)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Turn a doorknob?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Open a can or jar?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Tie a shoe lace?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Pick up a dime?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

The following questions are about how stroke has affected your ability to participate in the activities that you usually do, things that are meaningful to you and help you to find purpose in life.

<table>
<thead>
<tr>
<th>8. During the past 4 weeks, how much of the time have you been limited in...</th>
<th>None of the time</th>
<th>A little of the time</th>
<th>Some of the time</th>
<th>Most of the time</th>
<th>All of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Your work (paid, voluntary or other)</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>b. Your social activities?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>c. Quiet recreation (crafts, reading)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Active recreation (sports, outings, travel)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. Your role as a family member and/or friend?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Your participation in spiritual or religious activities?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. Your ability to control your life as you wish?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>h. Your ability to help others?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
9. Stroke Recovery

On a scale of 0 to 100, with 100 representing full recovery and 0 representing no recovery, how much have you recovered from your stroke?

100 Full Recovery
90
80
70
60
50
40
30
20
10
0 No Recovery
APPENDIX 8: EQ-5D-5L

Health Questionnaire

English version for Australia
Under each heading, please tick the ONE box that best describes your health TODAY

### MOBILITY
- I have no problems with walking around
- I have slight problems with walking around
- I have moderate problems with walking around
- I have severe problems with walking around
- I am unable to walk around

### PERSONAL CARE
- I have no problems with washing or dressing myself
- I have slight problems with washing or dressing myself
- I have moderate problems with washing or dressing myself
- I have severe problems with washing or dressing myself
- I am unable to wash or dress myself

### USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)
- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

### PAIN / DISCOMFORT
- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

### ANXIETY / DEPRESSION
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed

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• We would like to know how good or bad your health is TODAY.

• This scale is numbered from 0 to 100.

• 100 means the best health you can imagine.
  0 means the worst health you can imagine.

• Mark an X on the scale to indicate how your health is TODAY.

• Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = 

---

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