ASSESSMENT OF FLUOXETINE IN STROKE RECOVERY (AFFINITY) TRIAL

**Formal title:** An Australasian, investigator-driven, NHMRC funded, 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 5, 18th November 2015
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Funding:
National Health and Medical Research Council, Australia

Registration numbers:
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.

Name of Investigator at Participating site (Printed)

Name of Institution (Printed)

Site Investigator’s Signature Date (Day / Month / Year)

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Signature Date (Day/Month/Year)
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## 1. SUMMARY

| Title | An Australasian, investigator-driven, NHMRC funded, 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 | Assessment of fluoxetine in stroke recovery (AFFINITY) trial |
| Acronym | AFFINITY |
| Clinical phase | IIIb (i.e. fluoxetine is an established drug for depression, but not for stroke recovery; hence, possible new indication) |
| Trial Co-Principal Investigators | Associate Professor Maree Hackett, The George Institute for Global Health & The University of Sydney  
Professor Graeme Hankey, The University of Western Australia & Sir Charles Gairdner Hospital |
| Primary Research Question | Does treatment with fluoxetine, 20 mg once daily, started 2-15 days after stroke onset and continued for 180 days, improve functional outcome at 180 days after randomisation? |
| Trial design | Parallel group, randomised, placebo-controlled clinical trial. |
| Setting | Australian and New Zealand hospital stroke units and rehabilitation centres |
| Eligibility criteria | **Inclusion Criteria**  
Men or women aged ≥ 18 years with all of the following:  
- 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 (intracerebral and/or subarachnoid) 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 produce a modified Rankin Scale (mRS) score of >1 and to warrant treatment from the perspective of patient or carer(s).  

**Exclusion Criteria**  
Any of the following:  
- History of epileptic seizures  
- History of bipolar disorder  
- History of drug overdose or attempted suicide  
- Ongoing treatment with any selective serotonin reuptake inhibitor (SSRI)  
- Allergy or contra indication to fluoxetine including  
  - Hepatic impairment (serum alanine aminotransferase [ALT] >120 U/l),  
  - Renal impairment (creatinine >180micromol/l or eGFR < 30ml/min/1.73m²),  
  - Hyponatremia (sodium <125mmol/L) despite treatment of the cause and confirmed on repeat testing,  
- Use of medications that may interact seriously with fluoxetine  
  - Proposed use of a monoamine oxidase inhibitor (MAOI), or use of a MAOI within 14 days prior to randomisation  
  - Current treatment with an antipsychotic drug (neuroleptic), pimozide, tamoxifen, or tramadol, unless the patient, doctor and if possible prescribing doctor, believe it is appropriate to discontinue use.  
- Not available for follow up over the next 365 days e.g. no fixed home
Randomisation

Randomisation is by means of a password protected, computerised central randomisation service available 24 hours-a-day, using a minimisation algorithm to achieve balance between the two treatment groups for 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

Participants are randomly assigned to 180 days of treatment with either:

- Fluoxetine, 20mg capsules, to be taken once daily, or
- Placebo capsules that match the fluoxetine capsules, once daily.

For participants unable to swallow, the contents of an opened capsule can be given via enteral tube.

Outcome measures

**Primary outcome**

- Functional outcome as measured by the mRS using the simplified modified Rankin Scale questionnaire (smRSq) at 180 days after randomisation.

**Secondary outcomes at 180 and 365 days after randomisation**

- Survival,
- Mood (Patient Health Questionnaire-9 item [PHQ-9] [46]),
- Cognitive function (Telephone Interview of Cognitive Status [TICSm] [47]),
- Communication (Stroke Impact Scale [SIS] [48]);
- Motor function (SIS [48]);
- Overall health status (SIS [48]);
- Health-Related Quality of Life (HRQoL) (EuroQoL [EQ-5D-5L] [49]); and
- Functional ability (smRSq [44, 45]) at the 365 day assessment.

- New diagnosis of depression requiring treatment with antidepressants;
- Fatigue (vitality domain of the Short Form 36 item, SF-36 [50, 51]);

**Serious adverse events at any time during follow-up and which are also recorded as other secondary outcomes**

- New Stroke, ischaemic or haemorrhagic [not the qualifying event leading to enrolment]
- Acute coronary syndrome [Myocardial infarction confirmed by ECG and/or raised serum Troponin]
- Upper gastrointestinal bleed requiring blood transfusion and/or endoscopy
- Other major bleed (i.e. not upper GI or intracerebral) requiring blood transfusion or procedural intervention
- Fall
- New fracture [confirmed on X ray]
- Epileptic seizure [focal or generalised]
- Symptomatic hypoglycaemia [blood sugar < 3mmol/l]
- Symptomatic hyperglycaemia [blood sugar > 22mmol/l]
- New hyponatraemia [Na < 125mmol/l]
- Attempted suicide/self-harm
- Death

*Cost of health care over the first year*

| Follow up | At 28, 90, 180 and 365 days after randomisation. Participants are assessed by the site investigator at 28 and 90 days after randomisation, in the hospital ward, outpatient clinic or via telephone. Participants are followed-up at 180 and 365 days after randomisation by the trial coordinating centre, by telephone or postal questionnaire. |
| Sample size estimate | 90% power to detect an absolute increase in the proportion of participants with an mRS of 0-2 at 6 months from 50% to 57.5% |
| Number of participants | 1,600 (800 in each group) |
| Statistical methods | An ordinal logistic regression analysis of the mRS adjusted for baseline variables included in minimisation algorithm |
| Trial duration | 2013-2018 |

Figure 1. Flow summary of trial participants and assessments
### 2. LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL/IADL</td>
<td>activities of daily living/instrumental activities of daily living</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
</tr>
<tr>
<td>BDNF</td>
<td>brain derived neurotrophic factor</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>cGMP</td>
<td>current Good Manufacturing Processes</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CLOTS</td>
<td>Clots in Legs Or sTockings after Stroke</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CT</td>
<td>Computerised Tomography</td>
</tr>
<tr>
<td>CV</td>
<td>Curriculum Vitae</td>
</tr>
<tr>
<td>DALYs</td>
<td>Disability adjusted life years</td>
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<tr>
<td>DMC</td>
<td>Data monitoring committee</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical manual of mental disorders-fourth edition</td>
</tr>
<tr>
<td>EFFECTS</td>
<td>Swedish multicentre randomised placebo-controlled trial to establish the efficacy of fluoxetine in patients with a recent stroke</td>
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<tr>
<td>eGFR</td>
<td>Glomerular Filtration Rate</td>
</tr>
<tr>
<td>EQ-5D-5L</td>
<td>EuroQol 5 dimensions 5 levels</td>
</tr>
<tr>
<td>FLAME</td>
<td>FLuoxetine for motor recovery after Acute ischaeMic strokE</td>
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<tr>
<td>FMMS</td>
<td>Fugl-Meyer Motor Scale Score</td>
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<tr>
<td>fMRI</td>
<td>functional Magnetic resonance Imaging</td>
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<tr>
<td>FOCUS</td>
<td>Fluoxetine Or Control Under Supervision</td>
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<tr>
<td>GCP</td>
<td>Good clinical practice</td>
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<tr>
<td>GCS</td>
<td>Glasgow Coma Scale</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
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<td>GSK</td>
<td>GlaxoSmithKline</td>
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<td>HR</td>
<td>hazard ratio</td>
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<td>HREC</td>
<td>Health review ethics committee</td>
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<tr>
<td>HRQoL</td>
<td>Health Related Quality of Life</td>
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<tr>
<td>ICH</td>
<td>International conference on harmonisation</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational medicinal product</td>
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<tr>
<td>IQR</td>
<td>Interquartile Range</td>
</tr>
<tr>
<td>ISF</td>
<td>Investigator site file</td>
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<tr>
<td>MAOI</td>
<td>Monoamine oxidase inhibitors</td>
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<tr>
<td>mRS</td>
<td>modified Rankin Scale</td>
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<tr>
<td>NHMRC</td>
<td>National Health and Medical Research Council</td>
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<tr>
<td>NIHSS</td>
<td>National Institutes of Health Stroke Scale</td>
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<tr>
<td>OCSF</td>
<td>Oxfordshire Community Stroke Project</td>
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<tr>
<td>OD</td>
<td>once daily</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>pCREB</td>
<td>Phosphorylated cAMP response element binding</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>Patient Health Questionnaire-9 item</td>
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<tr>
<td>POISE</td>
<td>Psychosocial Outcome In Stroke</td>
</tr>
<tr>
<td>PISC</td>
<td>Participant Information and Consent Form</td>
</tr>
<tr>
<td>PPP</td>
<td>Pharmaceutical packaging professionals</td>
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<tr>
<td>QALY</td>
<td>Quality adjusted life year</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>RCTs</td>
<td>Randomised Controlled Trials</td>
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<tr>
<td>RR</td>
<td>risk ratio</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAR</td>
<td>Serious Adverse Reaction</td>
</tr>
<tr>
<td>SCAST</td>
<td>Scandinavian Candesartan Acute Stroke Trial</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SF-36</td>
<td>Vitality Subscale of the Short Form-36</td>
</tr>
<tr>
<td>SIADH</td>
<td>Syndrome of inappropriate anti-diuretic hormone</td>
</tr>
<tr>
<td>SIS</td>
<td>Stroke Impact Scale</td>
</tr>
<tr>
<td>smRSq</td>
<td>Simplified modified Rankin Scale questionnaire</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>TGA</td>
<td>Therapeutic Goods Administration</td>
</tr>
<tr>
<td>TICSm</td>
<td>Telephone Interview for Cognitive Status- m</td>
</tr>
<tr>
<td>TOAST</td>
<td>Trial of org 10172 in acute stroke treatment</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>VITATOPS</td>
<td>VITAmins TO Prevent Stroke</td>
</tr>
</tbody>
</table>
3. BACKGROUND

Long-term disability after stroke is common, and is the third most common cause of disability adjusted life years (DALYs)

About 60,000 Australians experience a stroke each year [1,2]. Thrombolysis, endovascular thrombectomy, antiplatelet therapy and stroke unit care facilitate the one-year survival of about 48,000 (80%) but 15,000-24,000 (30-50% of survivors) remain disabled [3-5]. In 2010, stroke was the third leading cause of disability-adjusted life years (DALYs) worldwide among 291 diseases and injuries [6].

Treatments that improve recovery and reduce disability after stroke are lacking

One reason for the substantial disability after stroke is a shortage of effective, safe, affordable and accessible interventions that facilitate functional recovery [7]. Numerous clinical trials have failed to translate promising experimental data into clinically effective therapies [8]. However, hope has been re-ignited by the publication of the results of the fluoxetine for motor recovery after acute ischaemic stroke (FLAME) trial in 2011 (see page 12) [9].

Fluoxetine is a promising neuroprotective and neuroregenerative agent

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) that is commonly used to treat depression. It is also a promising neuroprotective and neuroregenerative / neurorestorative agent.

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 serotoninergic inputs, and serotoninergic fibres innervate secondary motor structures such as the basal ganglia [10,11]. Second, SSRIs have a neurotrophic effect and stimulate neurogenesis in the adult brain [12-17]. They 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 [12-16], 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 [17]. Third, fluoxetine may have a neuroprotective role associated with its anti-inflammatory effect [18], 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 [19].

Human studies indicate that fluoxetine use may improve stroke recovery

Functional magnetic resonance imaging (fMRI) studies have found that fluoxetine can modulate motor activity in healthy subjects [20]. 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 [21]. These findings were replicated in a trial of 10 stroke patients [22]; participants who took a single dose of fluoxetine 20 mg showed increased muscle activation in the paretic arm. Among 52 post-stroke hemiplegic participants who were receiving physiotherapy and were randomly assigned to fluoxetine 20 mg daily, maprotiline 150 mg daily or placebo for 3 months, those assigned fluoxetine showed the greatest functional improvement as judged by a graded neurological scale and a measure of activities of daily living (Barthel Index) [23,24]. In another randomised trial, daily
administration of 10 mg of the SSRI citalopram to stroke patients for 4 months was associated with a reduction in neurological impairment National Institute of Health Stroke Scale (NIHSS) score (appendix 1) of 2.3 versus 3.5 control, p=0.03) at trial completion [25]. In another randomised trial of fluoxetine (n=32), nortriptyline (n=22) and placebo (n=29), three 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, after adjusting for age depression, stroke severity, and rehabilitation intensity [26]. The significant benefits of treatment, as measured by the mRS compared with placebo, continued for at least 1 year.

**The fluoxetine for motor recovery after acute ischemic stroke (FLAME) trial in humans.**

Among 118 patients with ischaemic stroke 5–10 days earlier, hemiparesis and a Fugl-Meyer Motor Scale Score (FMMS) < 55, random allocation to double-blind treatment with fluoxetine 20 mg daily (n=57) for 3 months, compared with placebo (n=56), improved motor function (adjusted mean FMMS 34.0 vs 24.3 points; p=0.003), functional independence mRS score of 0-2: 26.3% vs 8.9%; odds ratio [OR]: 3.8, 95% confidence interval [CI]: 1.2 to 10.7), and maintained participants free of depression (96% vs 71%; p=0.002) [9]. Adverse effects included transient nausea, diarrhoea, and abdominal pain (14 [25%] fluoxetine vs 6 [11%] placebo). Despite its encouraging results, the FLAME trial has raised several questions [27]:

1. Are the results of the FLAME trial valid?

Although systematic error was minimised by double-blinding and randomisation, random error might have occurred because of the small sample size (n=118) and limited statistical power.

Other studies in humans: a systematic review of all randomised controlled trials of fluoxetine In order to minimise random error and explore external validity (generalisability), we completed a Cochrane systematic review and meta-analysis of 52 randomised controlled trials (RCTs) of SSRIs on recovery after stroke in a total of 4,059 patients [26]. Overall, use of SSRIs was associated with less dependency (risk ratio [RR] 0.81, 95% CI: 0.68 to 0.97) (two trials, n=223) at the end of treatment compared with control (placebo or usual care) [28] (see Figure 2),

![Figure 2. Risk ratio of dependence, defined by modified Rankin Scale score (mRS score 3-5) [28].](image-url)
and less disability (standard mean difference 0.91, 95% CI: 0.60 to 1.22) (22 trials, n=1343) at the end of treatment compared with control (placebo or usual care) (see Figure 3) [28].

<table>
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<tr>
<th>Study or Subgroup</th>
<th>SSRI Mean SD</th>
<th>Total</th>
<th>Control Mean SD</th>
<th>Total</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
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<td>70.31</td>
<td>6.94</td>
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<td>Robinson 2000a</td>
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<td>79.8</td>
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<td>5.0%</td>
</tr>
<tr>
<td>Xu 2001</td>
<td>73</td>
<td>4.4</td>
<td>26</td>
<td>67.4</td>
<td>4.1</td>
<td>27</td>
<td>4.5%</td>
</tr>
<tr>
<td>Xu 2007</td>
<td>64.4</td>
<td>8.23</td>
<td>36</td>
<td>56.9</td>
<td>6.88</td>
<td>36</td>
<td>4.8%</td>
</tr>
<tr>
<td>Ye 2004</td>
<td>78.75</td>
<td>14.19</td>
<td>30</td>
<td>50.26</td>
<td>13.4</td>
<td>30</td>
<td>4.4%</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>511</td>
<td>68.3</td>
<td>11</td>
<td>697</td>
<td>177</td>
<td>31.7%</td>
<td>0.49 (0.17, 0.80)</td>
</tr>
</tbody>
</table>

Figure 3. Standard mean difference in disability between SSRI and control groups at the end of treatment.

However, the validity of these results is compromised by substantial heterogeneity among the trials ($I^2=86; p<0.0001$), methodological limitations (e.g. lack of blinding, incomplete outcome data), and clinical heterogeneity (e.g. many trials excluded aphasic and cognitively impaired patients). Further, adverse event data were inadequate to determine risks, only 7 trials (n=495) followed patients after treatment ended, and trials at low risk of bias reported smaller treatment effects.

Moreover, only 12 trials of fluoxetine were placebo-controlled in a total of only 682 patients, and an average treatment duration of only 7 weeks. Of these 12 trials, the primary outcome was disability (binary) in only one trial and functional recovery (continuous) in two trials; 5 trials assessed functional recovery as one of many secondary endpoints, and no trial followed-up patients beyond the treatment period.

A meta-analysis of the 6 placebo-controlled trials of fluoxetine which measured degree of functional recovery showed that in a total of 277 patients fluoxetine was associated with less disability compared with placebo (standardized mean difference: 0.35, 95% CI 0.03 to 0.61) [28].

These data are not sufficiently robust to be conclusive or to change clinical practice. However, they are sufficiently promising to warrant further evaluation of the effects of
fluoxetine on recovery after stroke. One or more large RCTs, conducted according to the world’s best standards, would reliably answer the question [29,30].

2. Are the results of FLAME & other trials generalisable to patients without severe hemiparesis?
The effect of fluoxetine in patients with mild to moderate hemiparesis, disabling non-motor neurological deficits and severe disability (NIHSS score >20) is uncertain.

3. Are the results of FLAME & other trials generalisable to non-motor outcomes?
The effects of fluoxetine on cognition, communication, quality of life, and fatigue are uncertain.

4. Do any beneficial effects of fluoxetine on recovery persist after it is stopped?
The effects of fluoxetine on recovery after fluoxetine is stopped have not been investigated yet.

5. Is the effect of fluoxetine on recovery due to antidepressant or neuroregenerative effects?
It is uncertain if there is an interaction between mood and recovery. The FLAME trial results remained significant after adjusting for depression [9], but in our systematic review the effect of SSRIs on recovery was greater in people with depression at randomisation [28]. Even if fluoxetine does improve recovery only because of its favourable effects on mood (e.g. less depression may facilitate participation in rehabilitation and increased physical and cognitive activity), that would still be an important finding that would change clinical practice.

6. Does the risk of serious adverse events offset or exceed any benefits of fluoxetine?
Our systematic review indicated that SSRIs, compared with placebo or usual care, were associated with a non-significant excess of seizures (RR 2.7; 95% CI 0.6-11.6) (7 trials, 444 participants), gastrointestinal adverse effects (RR 1.9; 0.9-3.8) (14 trials, 902 participants) and bleeding (RR 1.6; 0.2-13) (2 trials, 249 participants) [28]. Cohort studies, whilst prone to confounding and indication bias, have also reported that SSRI use is associated with increased risk of seizures, bleeding and hyponatraemia, particularly during the first 4 weeks of treatment [31-35].

Summary of fluoxetine as a promising neuroprotective and neuroregenerative agent
Our Cochrane review suggests that fluoxetine has promising effects on stroke recovery, perhaps via neuroregeneration [28]. Further, fluoxetine is widely known, available and affordable (AUS$4.50 per month; no longer patented). However, the data from our review are not sufficiently compelling to prove that fluoxetine improves functional recovery after stroke, that any effects are independent of its effects on mood, and that any possible favourable effects are not offset by serious adverse effects, particularly among older stroke patients taking antithrombotic agents [28]. As in several areas of medicine, clinical practice in stroke recovery has been influenced by premature reports of beneficial effects from small trials that have not been replicated by more methodologically robust studies [36-39]. It is not only ethical but also essential that sound large clinical trials are undertaken to provide valid and more precise estimates of the efficacy and safety of fluoxetine for post-stroke recovery and function [27,29,40-42]. Other leading investigators in the United Kingdom (UK) (GE Mead and MS Dennis), Sweden (E Lundström and the late V Murray) and United States of America (USA) also see the need for large RCTs [30,43]. The AFFINITY trial, whilst unique in many aspects, has been designed to allow future pooling of data with the concurrently ongoing UK Fluoxetine Or Control Under Supervision (FOCUS) trial (see section 15) and the
Swedish multicentre randomised placebo-controlled trial to establish the efficacy of fluoxetine in patients with a recent stroke (EFFECTS) trial (see section 15).

4. OBJECTIVES

Hypothesis
Administration of fluoxetine (20mg once daily; (od) for the first 180 days after stroke improves functional ability at the 180 day assessment, and the effect persists for 180 days after fluoxetine is stopped.

Primary Objective
To determine if treatment with fluoxetine, 20mg once daily, started 2-15 days after stroke onset and continued for 180 days, improves functional ability at the 180 day assessment as measured by the mRS using the simplified modified Rankin Scale questionnaire (smRSq) [44,45] (appendix 2).

Secondary Objectives
Secondary outcomes at 180 and 365 days after randomisation
- Survival;
- Mood (Patient Health Questionnaire-9 item [PHQ-9] [46]) (appendix 4);
- Cognitive function (Telephone Interview of Cognitive Status [TICSm] [47]) (appendix 5);
- Communication (Stroke Impact Scale [SIS] [48]) (appendix 7);
- Motor function (SIS [48]);
- Overall health status (SIS [48]);
- Health-Related Quality of Life (HRQoL) (EQ-5D-5L [49]) (appendix 8); and
- Functional ability (smRSq [44, 45]) at the 365 day assessment.
- New diagnosis of depression requiring treatment with antidepressants;
- Fatigue (vitality domain of the short form- 36 [SF-36] [50, 51]) (appendix 6).

Serious adverse events which occur at any time during follow-up and which are also recorded as secondary outcome measures include:
- New Stroke, ischaemic or haemorrhagic [not the qualifying event leading to enrolment]
- Acute coronary syndrome [myocardial infarction confirmed by ECG and/or raised serum Troponin]
- Upper gastrointestinal bleed [requiring blood transfusion and/or endoscopy]
- Other major bleed (i.e. not upper GI or intracerebral) requiring blood transfusion or procedural intervention
- Fall
- New fracture [confirmed on X ray]
- Epileptic seizure [focal or generalised]
- Symptomatic hypoglycaemia [blood sugar < 3mmol/l]
- Symptomatic hyperglycaemia [blood sugar > 22mmol/l]
- New hyponatremia [Na < 125mmol/l]
- Attempted suicide/self-harm
- Death

Cost of health care over the first year
Cost-effectiveness.
5. TRIAL PLAN AND PROCEDURES

Trial design
Parallel group, randomised, placebo-controlled clinical trial in which the participants, site investigators, and assessors will all remain unaware (i.e. blinded) of the intervention assignments throughout the trial (i.e. “double-blind” for centres where the site investigator and assessor are the same individual; “triple-blind” for centres where the site investigator and assessor are distinct individuals).

Setting and recruitment
Participants are being recruited in Australian and New Zealand hospital stroke units and rehabilitation centres by site investigators trained in relevant aspects of the trial by members of the trial coordinating centre. Screening, assessments and consent are conducted by the site investigator and data on randomised patients will be entered into a secure internet site. Recruitment began in January 2013 and is expected to cease at the end of 2017.

Participants

Inclusion criteria
Men or women aged ≥ 18 years with all of the following:
- 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 (intracerebral and/or subarachnoid) stroke (including normal computerised tomography (CT) brain scan)
- Persisting measurable focal neurological deficits (e.g. motor, somatosensory, visual, language, cognitive) present at randomisation and severe enough to produce a modified Rankin Scale (mRS) score of ≥1 and to warrant treatment from the perspective of patient or carer(s).

Exclusion criteria
Any of the following:
- History of epileptic seizures
- History of bipolar disorder
- History of drug overdose or attempted suicide
- Ongoing treatment with any selective serotonin reuptake inhibitor (SSRI)
- Allergy or contra indication to fluoxetine including
  - Hepatic impairment (serum alanine aminotransferase [ALT] >120 U/l),
  - Renal impairment (creatinine > 180 micromol/l or estimated Glomerular Filtration Rate [eGFR] < 30ml/min/1.73m²),
  - Hyponatremia (sodium < 125 mmol/L) despite treatment of the cause and confirmed on repeat testing,
- Use of medications that may interact seriously with fluoxetine
  - Proposed use of a monoamine oxidase inhibitor (MAOI), or use of a MAOI within 14 days prior to randomisation
  - Current treatment with an antipsychotic drug (neuroleptic), pimozide, tamoxifen, or tramadol, unless the patient, doctor and if possible prescribing doctor, believe it is appropriate to discontinue use.
- Not available for follow-up over the next 365 days; e.g. no fixed home address
- Life-threatening illness (e.g. advanced cancer) that is likely to reduce 365 day survival
- Pregnant, breast-feeding or of child-bearing potential and not using contraception
• Enrolled in another interventional clinical research trial involving an investigational product (medicine) or device.

Co-enrolment
Co-enrolment in another clinical trial of a medicinal or surgical intervention is not permitted because the other intervention could affect the primary outcome measure in AFFINITY and, because it is not assigned at random to the AFFINITY trial patients, it may confound the AFFINITY trial results. Co-enrolment in observational studies is acceptable.

Consent
It is the primary responsibility of the investigator at each participating site to obtain informed consent from participants to participate in the AFFINITY trial for 365 days using one of the approved methods outlined in section 9 of this protocol.

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

Minimisation
At the time of randomisation, the following six prognostic variables are collected: age, living alone, independence in activities of daily living before the stroke, the verbal component of the Glasgow Coma Scale (GCS) (as derived from the NIHSS), arm power, and ability to walk [52]. The trial website has a computer program installed that automatically calculates the probability of survival free of dependency at the 180 day assessment, based on the prediction model developed and validated by Counsell et al [52]. It is anticipated that about half of randomised patients will have a predicted probability of 0-15%, and the other half 16 to 100% of being independent at the 180 day assessment.

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

1. Delay between stroke onset and randomisation (2-8 vs 9-15 days). As spontaneous recovery may be quicker in the first week, we want to ensure that there is no substantial difference between treatment groups in the number of patients randomised in the first week, and also no difference between treatment groups in the number of patients randomised in the second week.
2. Presence of a motor deficit. To ensure the prevalence of patients with and without a motor deficit is equal in both treatment groups.
3. Presence of aphasia. To ensure the prevalence of patients with and without aphasia is equal in both treatment groups.
4. Probability of survival free of dependency at 6 months (0.15 vs 0.16-1.0) [52]. To ensure that at baseline, patients in each treatment group have equal probability of being alive and independent (mRS: 0-2) at the 180 day assessment.

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 randomisation, participants are 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.
At randomisation, the system automatically generates a treatment allocation in a ratio of 1:1 active drug (fluoxetine) or placebo. Participants are allocated an AFFINITY number and a treatment number, that corresponds to a treatment pack located at the local hospital pharmacy. An email notification is sent to the trial coordinating centre and the site investigator with the randomisation details (AFFINITY number and treatment number). The site investigator is then responsible for ensuring the randomisation notification and medication prescription are delivered to the local hospital pharmacy so the participant may commence the allocated treatment as soon as possible.

**Intervention**

Participants are randomly assigned to six months treatment with either:
- Fluoxetine, 20mg capsules, to be taken once daily, or
- Placebo capsules that match the fluoxetine capsules (in appearance (same colour and shape), weight and texture), to be taken once daily.

For participants unable to swallow, the contents of an opened capsule can be given via enteral tube.

The fluoxetine capsules are a Generic brand of capsule supplied by Pharmaceutical Packaging Professionals (PPP) PTY LTD in South Australia.

The placebo capsules are manufactured and bottled at PPP.

The bottles of active drug [fluoxetine] and placebo are 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 (current good manufacturing processes) dedicated warehouse at below 25 degrees celsius.

The trial coordinating centre is responsible for ordering the trial medication for the individual sites from PPP.

PPP distributes the AFFINITY trial medication usually in blocks of 10 treatment packs (5 active and 5 placebo) directly to the local pharmacy departments of the participating sites at the request of the trial coordinating centre. Each treatment pack consists of two bottles per participant (i.e. each bottle will contain a 90 day supply of 110 capsules of either fluoxetine or matching placebo). This includes an extra 20 capsules in each bottle to allow for delays in follow-up appointments or lost trial medication. Participating sites will instruct their hospital pharmacies to store the product under appropriate conditions (below 25 degrees celsius).

Site investigators will prescribe 180 days [6 months] supply of the trial medication by means of a local hospital prescription to be dispensed to the participant at baseline. The treatment packs are dispensed by the local hospital pharmacy. All treatment packs will be returned to the trial coordinating centre at the 180 day follow up where they will be counted and forwarded to PPP for destruction.

Participants are encouraged to minimise any unintentional non-adherence by using simple strategies, such as linking tablet-taking to the same time as other medication or having breakfast. It is the responsibility of each site investigator to ensure that accurate records of trial medication prescriptions are maintained.
Drug interactions

Metabolism of fluoxetine
Following oral administration, fluoxetine is well absorbed from the GI tract. Oral bioavailability is estimated to be at least 60-80%. Peak plasma concentrations occur within 6-8 hours following a single oral dose. Food does not affect the systemic bioavailability of fluoxetine but it delays the absorption by 1-2 hours (not clinically significant). 95% is bound to human serum proteins.

Fluoxetine appears to be extensively metabolized, likely in the liver, to norfluoxetine and other metabolites via isoenzymes of the cytochrome P450 system, including 2D6, 3A4, 2C9, 3A5, and 2C19.

Norfluoxetine, the principal active metabolite, is formed via N-demethylation of fluoxetine.

Fluoxetine has a slow elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration. Its active metabolite, norfluoxetine has an elimination half-life of 4 to 16 days after acute and chronic administration. The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation).

Genetic polymorphisms that may reduce the metabolism of serotonin (and thereby increase blood and brain concentrations of serotonin)
A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6) - they are referred to as poor metabolizers. When a poor metabolizer takes several doses of fluoxetine the fluoxetine may accumulate to higher than usual concentrations in the blood, resulting in a greater exposure to fluoxetine than occurs in patients who have normal activity of enzyme. This could lead to adverse drug reactions of fluoxetine including anorexia, nervousness, tremor, tachycardia, and seizures.

Drugs that may reduce the metabolism of serotonin (and thereby increase blood and brain concentrations of serotonin)
Medications that inhibit the enzyme CYP2D6, and thereby increase blood and brain concentrations of fluoxetine, include:

- Antiarrhythmic drugs: Amiodarone, Quinidine (a medicine for heart arrhythmias).
- Antipsychotic drugs: Haloperidol, Pimozide. Some evidence suggests a possible pharmacodynamic and/or pharmacokinetic interaction between some SSRIs and some antipsychotics, including possible elevation of blood levels of haloperidol and clozapine. Concurrent use of fluoxetine with pimozide increases the risk of QTc prolongation.

Drugs that may interact with fluoxetine to increase blood and brain concentrations of serotonin
Fluoxetine, which increases the amount of serotonin that can act on receptors in the blood and brain, may interact with other medications that also increase blood and brain concentrations of serotonin. This can lead to increased risk of serotonin syndrome, characterized by agitation, tremor, diaphoresis, hyperreflexia, and increased muscle tone. Medications that increase blood and brain concentrations of serotonin include:

- Atypical antipsychotics: Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasidone
- SSRI antidepressants: Clomipramine, Sertraline, Vortioxetine (not a SSRI, but increases serotonin).

Concurrent use of these medications with fluoxetine requires careful monitoring for signs and symptoms of serotonin syndrome and appropriate dose adjustment or discontinuation.
concentrations of serotonin [53]. These medications, which should be avoided with fluoxetine, include:

- Other SSRIs
- Tramadol and other synthetic opiates
- Triptans, such as sumatriptan (Imitrex®, GlaxoSmithKline (GSK))
- Tryptophan,
- Lithium
- MAOIs, such as phenelzine (Nardil®, Parke-Davis), tranylcypromine (Parnate®, GSK), and selegiline (Eldepryl®, Somerset; and others).
  1. The concurrent use of fluoxetine with MAOIs is contraindicated.
  2. After stopping MAOIs, fluoxetine should not be started until at least 14 days have elapsed (after stopping the MOAI).
  3. After stopping fluoxetine, MAOIs should not be started until at least 5 weeks have elapsed (after stopping the fluoxetine), since fluoxetine is slowly eliminated from the body; and
- The herbal remedy St John’s Wort (Hypericum perforatum) can potentially also increase the levels of serotonin.

**Consequences of an increase in blood and brain concentrations of serotonin (see also “Overdose” below)**

**Serotonin syndrome**

The potential consequence of co-administration of fluoxetine with serotonergic drugs (see above) is an increase in blood and brain concentrations of serotonin and a cluster of symptoms called the serotonin syndrome.

The symptoms and signs of serotonin syndrome include: restlessness, irritability, altered behaviour, confusion, shivering, fever/hyperthermia, diarrhoea, tremor, hyperreflexia, rigidity, clonus, myoclonus, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes that include extreme agitation progressing to delirium and coma.

**Effect of fluoxetine on the blood concentrations of other drugs**

**Inhibition of CYP2D6.**

Fluoxetine is also a potent inhibitor of the liver enzyme, CYP2D6. Hence, fluoxetine can alter the blood concentrations of other medications that are metabolized by CYP2D6, such as:

- Tricyclic antidepressants: amitriptyline, imipramine, and desipramine
- Antiepileptic drugs: carbamazepine, phenytoin and
- Antipsychotic drugs: thioridazine.
- Codeine

These drugs should be started at low dose in patients taking fluoxetine, otherwise toxicity with these drugs may arise.

In contrast, fluoxetine inhibits the conversion of codeine to its active form morphine and thereby diminishes the analgesic effect of codeine.

Similarly, fluoxetine, by inhibiting CYP2D6, also inhibits the conversion of tamoxifen to its active metabolite, thus reducing the amount of active drug to protect against breast cancer recurrence.
Inhibition of CYP2C9 and CYP2C19
Fluoxetine also inhibits the CYP2C9 and CYP2C19 enzymes and thereby may interfere with the elimination of many medications including warfarin (an anticoagulant) and phenytoin (an antiepileptic medication). The effects of these medications therefore require careful monitoring.

Potential Effects of Co-administration of Drugs Highly Bound to Plasma Proteins
Because fluoxetine is tightly bound to plasma proteins, the administration of fluoxetine to a participant 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.

Participant adherence and compliance
Participants are asked to keep a record of their use of the trial and other medication (e.g. concurrent/additional medications).

Participants are encouraged to adhere to (i.e. continue) the allocated treatment and are asked to record the dates and reasons of any temporary or permanent discontinuation.

Participants will also be encouraged to comply with (i.e. consistently take) the allocated trial medication. They are asked to keep their capsule bottles and any remaining capsules for return to the trial coordinating centre in Perth at the 180 day assessment so that the compliance rate (the ratio of taken doses to total possible doses) can be calculated.

Premature discontinuation of trial medication
Participants who choose to stop taking the allocated treatment are still followed up for study outcome measures as per the study protocol and included in the primary intention-to-treat analysis.

The reason(s) for stopping the trial treatment prematurely is/are recorded in the participants case report form (CRF).

If withdrawal results from a Serious Adverse Event (SAE), Serious Adverse Reactions (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR) the event is reported as per protocol (Please see section 7 of this protocol for more information regarding SAEs, SARs and SUSARs).

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

Emergency Un-blinding
Un-blinding is strongly discouraged.

In the event of an emergency, such as a suspected serotonin syndrome, discontinue the trial medication and treat the participant in the usual manner.

If an emergency occurs and un-blinding is required please contact your local hospital pharmacy who will contact the 24 hour un-blinding hotline on 1800 175 982, in Australia and [+61 438 356 411] in New Zealand, this service is provided by PPP. Your local hospital pharmacy is required to provide the participants AFFINITY treatment number to break the code and receive the treatment allocation i.e. active (fluoxetine) or placebo.

The trial medication must be discontinued after emergency un-blinding.
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 central nervous system (CNS) dysfunction, ranging from excitation to coma.

Cardiac and vital sign monitoring is recommended, along with general symptomatic and supportive measures.

No specific antitode 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 because fluoxetine is highly protein-bound.

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 the course benign.

Stopping the trial medication at the 180 day assessment (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.

Possible Side Effects of Fluoxetine
Adverse effects and suggested management (Adapted from reference [54])

<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 usually improve over time; 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; suggest sugarless gum or saliva substitutes</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>Common but often not asked about [Male and female]</td>
<td>Discuss participant’s willingness to continue trial medication in view of stroke diagnosis, possible positive effects of the medication and 6 month treatment regime. Short term use of sildenafil [males] could also be considered if clinically appropriate.</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. Monitor participant’s mood [Possible new diagnosis of depression.]</td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>Antidepressants may paradoxically increase suicidal thoughts in those aged under 30</td>
<td>Protocol specific assessment of the participant: includes the PHQ-9 assessment which asks about suicidal thoughts. No evidence exists that asking about suicide makes people more likely to harm themselves. Urgent clinical management of the participant with suicidal ideation is required.</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Often occurs when starting SSRIs</td>
<td>Monitor participant and reassure that symptoms usually subside.</td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>Particularly a problem in the elderly and more common with SSRIs</td>
<td>Check sodium levels if the patient is symptomatic and treat clinically. Stopping the trial medication should</td>
</tr>
</tbody>
</table>
### Adverse effect | Comment | Management
--- | --- | ---
Serotonin syndrome | Characterised by changes in mental state (e.g., confusion or agitation), autonomic instability (e.g., high temperature, shivering, sweating, changes in blood pressure), and neuromuscular hyperactivity (e.g., clonus or hyper-reflexia). Seen particularly with SSRIs and other drugs that effect serotonin. | not be necessary unless symptoms persist. Stop the trial medication. Use supportive measures such as hydration, management of hyperthermia, and benzodiazepines. Consider cyproheptadine or chlorpromazine in severe cases.
Discontinuation syndrome | More common with SSRIs that have a short half-life (e.g., paroxetine or venlafaxine) | Advise the participant that fluoxetine has a long half-life and, as such, reducing dosage prior to discontinuation is not considered necessary.

**SSRIs=selective serotonin reuptake inhibitors.**

**Return and disposal of unused medication at the end of the treatment phase (180 day follow up)**
All unused medication is returned to the trial coordinating centre in Perth for medication accountability and from there returned to PPP for disposal.

Returns will be coordinated by the trial office in Perth by secure express post.

**Lost trial medication / Replacement stock**
The trial coordinating centre will liaise with Pharmaceutical Packaging Professionals [PPP], supplying them with the participants AFFINITY and treatment allocation numbers and the details of the participating site’s pharmacy for shipment of the replacement trial medication. The trial coordinating centre will liaise with the site Principal Investigator or their delegated staff so that the replacement medication can be prescribed and dispensed to the participant.
6. TRIAL ASSESSMENTS, MEASUREMENTS, ENDPOINTS

*Figure 4: Flow diagram summarising the process of the AFFINITY trial*

**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: Site Telephone/Face to Face assessment on treatment

Survival, living arrangements, clarification of the final diagnosis and cause of qualifying stroke, current medications, medication compliance, serious adverse events, pregnancy (female participants of child bearing age), primary outcome (smRSq), current depression, mood (PHQ-9),

↓

90 +/- 14 days: Site Telephone/Face to Face assessment on treatment

Survival, living arrangements, current medications, medication compliance, serious adverse events, pregnancy (female participants of child bearing age), primary outcome (smRSq), current depression, mood (PHQ-9),

↓

180 +/- 14 days: Central Telephone/Postal assessment at end of treatment

Survival, living arrangements, current medications, medication compliance, serious adverse events, pregnancy (female participants of child bearing age), health care utilisation, primary outcome (smRSq), current depression, mood (PHQ-9), cognition (TICSm), Fatigue (vitality subscale of SF36), health-related quality of life (EQ-5D-5L), overall health status (SIS),

↓

365 +/- 14 days: Central Telephone/Postal assessment at end of follow-up off treatment

Survival, living arrangements, current medications, serious adverse events, pregnancy (female participants of child bearing age), health care utilisation, primary outcome (smRSq), current depression, mood (PHQ-9), cognition (TICSm), Fatigue (vitality subscale of SF36), health-related quality of life (EQ-5D-5L), overall health status (SIS),

**Baseline assessment (2-15 days after stroke onset) (appendix 9)**

Prior to randomisation, the following are recorded: gender, date of birth, ethnicity, marital status, living arrangements, employment status, independence in activities of daily living before stroke, date of stroke, previous history of depression*, co morbidities, medications, classification of clinical stroke type (Oxfordshire Community Stroke Project, OCSP [55]) (appendix 3) ischaemic stroke subtype (Trial of Org 10172 in Acute Stroke Treatment [TOAST] criteria [56]), neurological impairments (NIHSS [57]); arm strength; ability to walk; functional ability (smRSq [44,45]), mood (PHQ-9 [46]), and the results of laboratory tests (serum creatinine, eGFR, sodium, ALT; pregnancy test if premenopausal woman; see below).
A history of “previous depression requiring previous treatment” is recorded at baseline. This should refer to a clinical diagnosis made by a GP, psychologist or hospital clinician prior to enrolment in AFFINITY. The responses to these questions should be completed before, and are independent of, the subsequent completion of the PHQ-9 and the associated score.

**Baseline Laboratory Tests**
A pregnancy test is performed on pre-menopausal women to confirm eligibility for the trial. Pregnant participants are excluded.

The following blood tests are performed at baseline and determine the eligibility of the participant for the trial.

Participants are excluded if:

- The ALT enzyme is 3 or more times above the upper limit of normal (> 120U/l)
- The serum creatinine is > 180micromol/l
- eGFR is < 30ml/min/1.73m²
- Blood sodium concentration is low (< 125mmol/L)

If the participant has an abnormal blood result at this baseline test please treat the cause, repeat the test and reassess before randomising. Laboratory tests completed within 15 days post stroke onset are accepted as baseline measures.

**Randomisation**
The trial medication is dispensed and administered.

The contact sheet containing participant and GP contact details for central follow up is completed and filed in the participant AFFINITY folder.

The site will then be required to send a letter to the participant’s GP, including details of the trial, management guidelines and the trial coordinating centre contact details.

Participants will also be asked to keep a record of any hospitalisations over the duration of the trial.

**28 and 90 day follow-up (appendix 9)**
At 28 days +/- 7 days and the 90 day +/- 14 days after randomisation, the participant will undergo a telephone or face to face interview with the randomising site staff to assess survival, living arrangements, clarification of the final diagnosis and cause of stroke (28 day follow-up only), current medications, medication compliance and tolerance, SAEs, pregnancy (female participants of child bearing age), primary outcome (mRS [44,45]), recent depression, and current mood (PHQ-9 [46]).

- Routine blood tests are not required
- Repeat blood tests (ALT, creatinine, eGFR and Blood sodium) may be necessary if the investigator deems it to be clinically indicated (ie the participant is clinically unwell and is displaying possible side effects of the trial medication [fluoxetine]).

If the blood sodium concentration during follow-up is low (<125mmol/L, the cause of the hyponatraemia may be syndrome of inappropriate anti-diuretic hormone (SIADH) secretion.

If SIADH is confirmed, by low plasma sodium concentration and osmolality and an inappropriately high urinary osmolality, the recommended treatment is to treat or remove the cause (if it is known) and restrict fluid intake to 800ml-1 Litre per day until the blood sodium concentration returns to normal.
As Fluoxetine may cause SIADH, and the AFFINITY trial medication may contain fluoxetine (or placebo), it is recommended that the AFFINITY Trial medication should be withheld until the blood sodium concentration has returned to normal (e.g. within 3-7 days of fluid restriction).

Once the sodium concentration has returned to normal, the AFFINITY trial medication can be re-started if the patient is willing to take it again.

If the SIADH reoccurs, then the trial medication should be ceased permanently and this should be reported to the AFFINITY trial office.

**Completion of the 90 day follow up:**
When the 90 day follow up assessment has been completed and the participant contact details have been received by the trial coordinating centre, a letter of introduction will be sent to the participant from the trial coordinating centre, with the contact details of the trial coordinating centre.

The letter will also advise participants to notify their GP or specialist of their participation in the AFFINITY trial, and to raise any concerns they may have regarding their participation in the trial with their GP, specialist and/or the trial coordinating centre. Participants will also be advised to report any temporary or permanent discontinuations of the trial medication to the trial coordinating centre and will be advised regarding forthcoming central follow up at the 180 and 365 day assessments including the procedure for the return of trial medication on completion of their allocated treatment.

**180 and 365 day follow-ups (appendix 9)**
At 180 days +/- 14 days and at 365 days +/- 14 days the participant will be followed up centrally by means of a telephone interview with trial coordinating centre staff to assess survival, living arrangements, current medications, medication compliance (180 day follow-up only), SAEs, pregnancy (female participants of child bearing age), health care utilisation, primary outcome (mRS [44,45]), recent depression, current mood (PHQ-9 [46]), cognition (TICSm [47]), fatigue (vitality subscale of SF36 [50,51]), health-related quality of life (EQ-5D-5L [49]) and overall health status (SIS [48]). The (SIS) can be delivered as a postal questionnaire.

<table>
<thead>
<tr>
<th>Table 1. Trial assessment schedule</th>
<th>Baseline</th>
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<th>90 Day</th>
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</table>
Outcome Measures

Primary Outcome
The primary outcome is functional ability 180 days after randomisation, as measured by the modified Rankin Scale (mRS), using the simplified modified Rankin Scale questionnaire (smRSq). The mRS is a simple, reliable and valid 6-point measure of functional outcome commonly used as the primary outcome in most stroke treatment trials. The mRS is measured at baseline (pre and post stroke scores are recorded), 28, 90, 180 and 365 day assessments.

The mRS is derived from the smRSq assessment which consists of 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. Are you able to do everything you were doing right before your stroke, even if slower and not as much?
3. Are you able to 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 mRS 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.

Secondary Outcomes
Secondary outcome measures, recorded at follow-up assessments 28, 90, 180 and 365 days after randomisation are:

- Survival
  Survival is recorded at the 28, 90, 180 and 365 day assessments.
  If the participant has died, details of the event including the date and cause of death are recorded as an outcome event on the SAE form.
- **Mood**
  Mood is assessed at baseline, and at 28, 90, 180 and 365 days after randomisation, by completing the PHQ-9 [46], which scores each of the 9 Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria [58] as ‘0’ (not at all) to ‘3’ (nearly every day), generating a total score from 0-27. Scores ≥ 15 indicate significant depressive symptoms requiring treatment. The PHQ-9 has been validated for use in stroke patients and can generate a DSM-IV equivalent diagnosis [58].

- **New diagnosis of depression requiring treatment:**
  A new clinical diagnosis of depression refers to, treatment for depression and prescription of an antidepressant since the previous assessment, therefore recorded at the 28, 90, 180 and 365 day assessments. This should refer to a clinical diagnosis made by a GP, psychologist, psychiatrist or hospital clinician since enrolment in the AFFINITY trial.

  The responses to the following questions (which form part of the assessment of a new clinical diagnosis of depression at all follow up visits) should be completed before, and are independent of, the subsequent completion of the PHQ-9 and the associated score.

  a. Has the patient been diagnosed with depression since the last assessment?
  b. Has the patient been treated for depression since the last assessment? (non-pharmacological)
  c. Has the patient been prescribed an antidepressant drug for treatment of depression since the last assessment?

  Note: (b) Treatment non pharmacological can include psychotherapy, herbal remedies and other non-pharmacological therapies and electroconvulsive therapy.

- **Fatigue**
  Fatigue is assessed at 180 and 365 day assessments by completing the vitality subscale of the full SF-36 [50,51].

- **Cognitive function**
  Cognition is assessed at 180 and 365 day assessments using the TICSm, which scores 13 items (including orientation, recent and delayed memory, attention and comprehension) to a maximum possible score of 39 [47]. The TICSm has been validated in stroke patients and can be administered face-to-face or via telephone.

- **Communication, motor function and overall Health Status**
  Communication, motor function, and overall health status is assessed at the 180 and 365 day assessments by the SIS [48], which measures 8 health domains (strength, hand function, activities of daily living/instrumental activities of daily living (ADL/IADL), mobility, communication, emotion, memory and thinking, participation). It has been evaluated successfully for use by proxy respondents [59].

- **Health-Related Quality of Life (HRQoL)**
  Health related quality of life is assessed at the 180 and 365 day assessments by completing the EQ-5D-5L [49], a standardised instrument that provides a simple descriptive profile and a single index value for health status.

- **Functional ability**
  The simplified modified Rankin Score (smRSq [44,45] is assessed at the 365 day assessment to ascertain if any beneficial effects of fluoxetine on recovery persist after it is stopped.

  **Serious adverse events and secondary outcome events**
Assessed and recorded at the 28, 90, 180 and 365 day assessments.

- New Stroke, ischaemic or haemorrhagic [not the qualifying event leading to enrolment]
- Acute coronary syndrome [MI confirmed by ECG and/or raised serum Troponin]
- Upper gastrointestinal bleed requiring blood transfusion and/or endoscopy
- Other major bleed (i.e. not upper GI or intracerebral) requiring blood transfusion or procedural intervention
- Fall
- New fracture [confirmed on X ray]
- Epileptic seizure [focal or generalised]
- Symptomatic hypoglycaemia [blood sugar < 3mmol/l]
- Symptomatic hyperglycaemia [blood sugar > 22mmol/l]
- New hyponatremia [Na < 125mmol/l]
- Attempted suicide/self-harm
- Death

- **Health care utilisation**
  Assessed at the 180 and 365 day follow-ups by asking participants and using data linkage to provide information on hospital admissions, outpatient visits, days spent in care homes, health care visits and services utilised.

**Other Measures**

**Trial Medication Adherence**

Adherence is 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 participants 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 the trial medication, and dates of and reasons for stopping are recorded. Analysis of medication adherence will compare groups based on the reported non-adherence and number of residual tablets.

**Trial Medication Cessation**

Medication cessation is recorded as temporary or permanent, together with dates and reasons for stopping.

**Concurrent antidepressant medication**

Participants are asked if they have been started on any antidepressant medication since enrolment (if yes, which drug(s) and indication).

**7. SERIOUS ADVERSE EVENTS/REACTIONS**

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 [60, 61].
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% [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) [61].

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 [61]. 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 [61].

Irrespective of whether fluoxetine treatment is administered or not, about 20% of hospitalised 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 not it is 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 is provided and 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;
• results in a secondary outcome event for the AFFINITY Trial (New stroke, ischaemic or haemorrhagic [not the qualifying stroke leading to enrolment], Acute coronary syndrome [MI confirmed on ECG and/or raised serum Troponin], Upper gastrointestinal bleed requiring blood transfusion and/or endoscopy, Other major bleed (i.e. not upper GI or intracerebral) requiring blood transfusion or procedural intervention, New fracture [confirmed on X Ray], Epileptic seizure [focal or generalised], New hyponatraemia [Na<125mmol/l], Attempted suicide/self-harm).

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 hospitalisation is to be considered an SAE only if it is an official admission. In addition, a hospitalisation 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 are recorded from the time of consent until the end of follow-up. SAEs, SARs and SUSARs will also be assessed at the 28, 90, 180 and 365 day assessments.

If the event is serious and/or related to the trial medication it must be reported to the trial coordinating centre immediately (within 24 hours) of the site investigator becoming aware of the event. This is done by completing the serious adverse event form [Hard Copy] and then entering the information on the web-based CRF. If for any reason the web –based system cannot be accessed, the site investigator will need to fax the completed hard copy to the trial coordinating centre.

The site investigator is also responsible for reporting any SAEs, SARs and SUSARs that their participants may experience to the Lead Human Research Ethics Committee (HREC) responsible for their site immediately (within 24hrs) of becoming aware of the event and according to their local guidelines.

SUSARs are reported according to regulatory requirements to the Therapeutic Goods Administration (TGA) in an expedited manner by the trial coordinating centre when a report is received from a site, the initial report is due within 7 calendar days of receipt of the event if the event is fatal or life threatening, with a follow up report within a further 8 days or within 15 calendar days of receipt of the event for non-fatal, non-life threatening events.
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.

The trial coordinating centre will collate all SAEs, SARs and SUSARs that occur in the trial and submit 6 monthly reports to the lead HRECs as applicable. Site investigators will also receive copies of these reports and are responsible for submitting them to their local research governance office as per local guidelines.

**Monitoring Side Effects and Interactions of fluoxetine**

Participants are assessed 28 days after baseline to monitor for drug safety and SAEs and are clinically managed as appropriate. Any reported unexpected serious adverse events are discussed with one of the trial clinicians and the participant’s GP. This information is used to guide a decision regarding their continuation on the trial medication. In addition, we will provide all participants and their GPs with a list of common serious adverse effects and drug interactions.

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

**Depression**

Pre-existing (prevalent) depression is common amongst stroke patients. Subsequent (incident) depression is also common after stroke, occurring in around a third of stroke survivors.

Depression may be detected during the AFFINITY trial:

1. At the baseline assessment, before randomisation by a score of 15 or greater on the PHQ-9 test.
2. During one of the AFFINITY trial follow-up assessments by a score of 15 or greater on the PHQ-9
3. During a visit to the participant’s general practitioner (GP) or another clinician e.g. physician

After randomisation in the AFFINITY trial, participants are advised to inform their GP and any treating clinician that they are participating in a clinical trial and taking either fluoxetine 20mg or a placebo daily.

After randomisation, the site will send a letter to the GP of each participant. If there is no regular GP, participants are encouraged to nominate one. The letter provides information about the duration of the trial, medications to avoid due to potential interactions with fluoxetine, and suggestions on the management of a major depressive episode during the trial follow up period.

During the course of the trial, the AFFINITY trial coordinating centre will alert GPs if their patient displays moderate/severe depressive symptoms (PHQ-9 score ≥ 15) during any follow-up assessments.

Some suggestions for managing depression in the AFFINITY trial are:

**A. Prevalent (existing) depression**: patients who are depressed before/at the time of randomisation.

1. If the patient is already taking an antidepressant medication and wishes to participate in the AFFINITY trial, the treating clinician should discuss with the patient and if possible the prescribing clinician whether or not it is possible and appropriate to discontinue the antidepressant (and perhaps start non-pharmacological treatment [e.g. clinical psychologist; see below] for the depression) before randomisation (to fluoxetine 20 mg, or placebo, daily) in the AFFINITY trial.
Most antidepressants can be titrated down to zero over 5-7 days, but the treating clinician should check with their local pharmacy regarding specific guidelines for individual antidepressants. When the patient has been titrated off the current antidepressant they should then have a further 2-3 days free of medication before starting the AFFINITY trial medication.

2. If the patient is not being treated for depression but warrants it, and wants to participate in the AFFINITY trial, consider non-pharmacological treatment for the depression (i.e. referral to a clinical psychologist; see below) before randomisation in the AFFINITY trial.

Clinical psychology can be accessed through the Medicare Better Access initiative and is available to Australian residents and citizens. There is provision for up to 10 rebated sessions per year as part of a GP mental health treatment plan (http://www.health.gov.au/mentalhealth-betteraccess).

B. Incident (new) depression: patients who develop depression after randomisation

0-6 months after randomisation
If the patient develops depression after randomisation in the AFFINITY trial and during the first 6 months of follow-up, whilst taking the AFFINITY trial medication (fluoxetine 20 mg, or placebo, daily)

1. Consider non-pharmacological treatment for the depression if appropriate, such as advising an increase in social outlets, regular exercise or referral to a clinical psychologist.
   1a. Clinical psychology can be accessed through the Medicare Better Access initiative and is available to Australian residents and citizens.
   1b. There is provision for up to 10 rebated sessions per year as part of a GP mental health treatment plan (http://www.health.gov.au/mentalhealth-betteraccess).

2. If the treating clinician feels that antidepressant medication is necessary, consider the following:
   2a. Commence treatment with an antidepressant that is NOT an SSRI, in addition to the AFFINITY trial medication.
      ➢ The patient should be informed about the possibility of an interaction between the prescribed antidepressant and the AFFINITY trial drug (if fluoxetine), and the nature of symptoms of serotonin toxicity (which include confusion, sweating, unsteadiness, shaking, and diarrhoea) and hyponatraemia (confusion, seizures). The patient should be monitored regularly for the above symptoms and, if hyponatraemia is suspected, undergo a blood test for plasma sodium concentration.
   2b. Consider referral to (or consultation with) a specialist psychiatrist.

6-12 months after randomisation
If the patient develops depression 6-12 months after randomisation in the AFFINITY trial, after having ceased the AFFINITY trial medication,

1. Consider non-pharmacological treatment for the depression if appropriate, such as advising an increase in social outlets, regular exercise or referral to a clinical psychologist.
   1a. Clinical psychology can be accessed through the Medicare Better Access initiative and is available to Australian residents and citizens.
   1b. There is provision for up to 10 rebated sessions per year as part of a GP mental health treatment plan (http://www.health.gov.au/mentalhealth-betteraccess).
2. If the treating clinician feels that antidepressant medication is necessary, consider the following:
   2a. Commence treatment with an antidepressant that is NOT an SSRI
   2b. Consider referral to (or consultation with) a specialist psychiatrist.

8. STATISTICAL METHODS

Primary analysis
The primary analysis will compare the mRS scores at the 180 day assessment for each treatment group by an ordinal logistic regression analysis, after adjusting for any baseline imbalance between the treatment groups in factors included in the minimisation algorithm [62, 63]. The analysis will retain participants in the treatment groups they were originally allocated to [64, 65].

Secondary analyses
The main secondary analysis will compare, in each treatment group, at the 365 day assessment the mRS scores by means of an ordinal logistic regression analysis. Other secondary analyses will compare, in each treatment group, at 180 and 365 day assessments: the proportion of participants who are functionally independent according to the mRS score (0-2) by means of dichotomized outcome analysis, functional independence after controlling for survival (Cox proportional hazards model), mood (changes in PHQ-9 scores and proportion with PHQ-9 ≥ 15 [46]), cognition (TICSm scores [47]), communication (SIS [48]), motor function (SIS [48]), overall health status (SIS [48], HRQoL (EQ-5D-5L [49], new diagnosis of depression requiring treatment with antidepressants, fatigue (vitality domain of the SF-36 [50, 51]), medication adherence and cessation, and SAEs/SARs.

Economic analyses
An economic evaluation is 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. Inpatient and outpatient costs, including the study drug, are estimated from each assessment and are costed using standard published rates (e.g. from Medical Benefits Schedule for non-hospital medical services, Pharmaceutical Benefits Schedule for prescribed medications and Australian Refined-Diagnostic Related Groups cost weights for hospital services). The average costs incurred by participants in both treatment groups are calculated.

Average HRQoL scores at the 365 day assessment for each participant are estimated and weighted by survival up to 365 days to determine a measure of QALY post-stroke. The average of this measure for participants in each treatment group is estimated to determine the incremental QALY gain/loss from the intervention and, when set alongside data on costs, will enable estimation of an incremental cost-effectiveness ratio. Sensitivity analysis will test uncertainty in key parameters (e.g. selection of cost weights and statistical variation in HRQoL scores).
Descriptive statistics
For descriptive purposes baseline characteristics are presented by treatment groups. Discrete variables are 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 are graphically analysed (i.e. box plots) to determine if variances between groups are equal and variables with unequal variances are transformed (e.g. log transformation) where necessary to ensure that any difference in coefficients are true differences.

Sample size
The AFFINITY trial will recruit 1600 participants over 4 years. Based on data from the Clots in Legs Or sTockings after Stroke (CLOTS) trial [66] and the Scandinavian Candesartan Acute Stroke Trial (SCAST) [67], we expect the proportion of participants not dependent on others (as indicated by a score of 0-2 on the mRS [44]) to be 50% in the AFFINITY control group 180 days after randomisation (see Table 2).

Table 2. Expected distributions of smRSq scores at the 180 day assessment

<table>
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<th>smRSq score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<th>6</th>
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<td>Control group</td>
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<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 the odds of being functionally independent (mRS 0-2) at the 180 day assessment 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) [9]. An odds ratio of 1.35 is equivalent to an increase in the proportion of participants being functionally independent at the 180 day assessment 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 [68] and 90% power, the trial will require 1600 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 at least 1440 participants completing follow-up, 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 [69, 70].

The target of 1600 are reviewed by the blinded steering committee taking account accruing data on the distribution of participants (across both treatment groups) between different mRS 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.

9. ETHICS

Declaration of Helsinki, National Statement, International Conference on Harmonisation Good Clinical Practice (ICH-GCP) Guidelines
The trial is performed in agreement with the Declaration of Helsinki and in accordance with relevant national and international regulatory and ethical frameworks.
Ethics review and approval
It is the responsibility of the investigator at each participating site to obtain written approval from their relevant ethics committee and regulatory bodies before starting the trial. This documentation must be filed in the investigator site file (ISF) provided by the trial coordinating centre.

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

The site investigator is responsible for ensuring informed consent is obtained from the participant before any protocol specific procedures are carried out.

Participants will receive oral and written information about the trial. The current ethics approved version of the participant information and consent form is provided for review to all potential participants. The oral explanation to the participant is performed by the site investigator or designated person, and covers all the elements specified in the participant information sheet and consent (PISC) form.

The participant is given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. Sufficient time is given to the participant to consider the information provided and discuss the trial with their relatives if they wish.

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

Participants are asked to consent to being randomly allocated to fluoxetine or placebo capsules that are taken once daily for 180 days, in conjunction with four follow-up assessments over a total period of 365 days. The follow-up of participants has not been extended beyond the 365 day assessment at present. However it is possible that as the trial progresses and the results of the preliminary analyses become available, the steering committee may decide that it may be of scientific value to follow-up participants for five years. This would provide information on the possible beneficial long term treatment effects of fluoxetine. If this occurs we will notify the participant and ask for their consent to this extended follow-up.

The site investigator or delegated member of the trial team and the participant will sign and date the informed consent form to confirm that consent has been obtained. The original copy of the informed consent form is filed in the ISF for inspection by the trial monitor, a copy is given to the participant and a copy is filed in the participants medical records.

Withdrawal of Consent
Participants can withdraw from the trial at any time without loss of benefits to which they would otherwise be entitled. This process is clearly documented in the PISC form. All participant withdrawals need to be documented in the participant’s medical records, on the withdrawal of consent form and entered onto the online web based system.

Waiver of Consent/Next of Kin/Person responsible/Legal surrogate
In Australia and New Zealand, the rules and system differ in every state regarding the appointment and powers of guardians, and consent to medical treatment by persons other than the participant. In all the states, the intention behind the legislation is the protection of the rights, welfare, freedom of decision and action, and interests of the person involved.
The laws and definitions for the terms ‘waiver of consent’, ‘next of kin’, ‘person responsible’ and ‘legal surrogate’ in the context of a clinical trial may also differ between States and Territories in Australia and New Zealand, therefore the specific wording should be checked in each region and specific local ethics approval obtained.

**Data protection and retention**

All trial documentation is stored in a secure environment for a minimum of 15 years with all personal identifiers removed following trial closure, according to regulatory and ethical requirements.

**10. GOVERNANCE**

**Insurance and Indemnity**

Sites participating in the trial will seek insurance or indemnity to cover their liability from their local institution.

**11. 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 site 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 assessment.

Original PISC forms and the 28 and 90 day follow up CRF will be kept at the individual hospital site. Original consent forms must be filed in the ISF. 180 day and 365 day original CRF’s will be kept at the trial coordinating centre.

Site personnel will be trained at site initiation on completion, collection and retention of adequate and accurate source documents. Source documents verify the authenticity of data recorded on the electronic CRFs and that the trial was carried out in accordance with the protocol. In the event of an on-site monitoring visit or a regulatory body audit these documents must be produced by the site for review.

At completion of the trial, the trial coordinating centre 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 a minimum of 15 years).

**Selection and monitoring of participating centres**

Potential centres are assessed by the trial coordinating centre to confirm they have adequate facilities and medical resources to conduct the trial. Prior to commencement of the trial at selected sites all designated research staff including the site investigator, co-site investigator(s) and Research Nurse(s) are trained in the methods of the trial at site initiation, which is held by teleconference.

Pharmacy specific initiations will be conducted via teleconference with pharmacy staff participating in the trial. This will include training on the protocol and all procedures and requirements for management of the trial medication; supply, storage, dispensing, returns, and all associated record keeping.

Prior to site initiation all the necessary ethical and regulatory approvals will be in place and copies of the associated documents will be held by the trial coordinating centre and filed on site in the investigator and pharmacy site files. The site investigator, co-site investigator(s),
Research Nurse(s) and pharmacist(s) will sign and provide up-to-date Curriculum Vitae(s) (CVs) (maximum of two pages) to the trial coordinating centre along with a copy of the signed delegation of duties log.

Participating sites will be monitored using a risk based model, consisting of centralised monitoring of the eCRF by the trial coordinating centre and statistical data monitoring as follows:

Centralised Monitoring of eCRF
- Site acknowledgement that written informed consent (waiver of consent, next of kin, person responsible or legal surrogate if applicable) has been obtained from the participant according to the protocol is required to be documented for each participant on the source baseline assessment form which is then submitted on the eCRF.
- Participant information submitted on the eCRF will be screened for missing and inconsistent data. Queries will be raised and resolved directly with the site via the electronic interactive query report system, email and telephone.
- Participant follow up will be monitored continually for submission within the specified time parameters and contact made directly with the site if not received.
- Monitoring / Adjudication to a standard of 100% will be centrally managed for all reported: Serious Adverse Events, Protocol Violations, Pregnancy Notifications and Withdrawal of Consent

Statistical Data Monitoring
- The number of events by site as follows: serious adverse events, protocol violations, lost to follow up, withdrawn participants, will be monitored to identify unusually high or low numbers of reported events at individual sites.
- Unusually high numbers of late form submissions at individual sites.
- Unusually high numbers of missing data at individual sites.

Note: Unusual findings may flag the need for specific on site monitoring visits which will be carried out by the trial coordinating centre.

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 is followed as specified. Protocol deviations are documented on a protocol violation form and entered onto the online data eCRF system, on submission of the form an email is sent to the trial coordinating centre. The hard copy is stored in the participant’s site 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 site investigator to submit this to each HREC for written approval. The approval letter, signed by the HREC chair, must refer specifically to the site 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 investigator at each participating site.**

It is the responsibility of the investigator at each participating site 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 waiver of consent, next of kin, person responsible or legal surrogate) before any protocol specific procedures are carried out;
- ensure participants are managed in accordance with ICH-GCP guidelines;
- report any protocol violations and SAEs to their local hospital ethics committee and to the trial coordinating centre immediately and;
- report any protocol amendments, safety and DMC reports to their local hospital Ethics/regulatory bodies.

**Auditing by regulatory bodies**

The trial may be audited by inspectors appointed by government regulatory authorities. CRFs, medical records, source documents and other trial files must be accessible at all trial sites at times of 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

**Trial withdrawal by a site investigator**

If a site investigator withdraws from the trial prematurely, they are asked to:

- Provide their local ethics committee, regulatory bodies and the trial coordinating centre with a written statement describing why they have withdrawn from the trial. (File a copy of this letter and acknowledgement received from the HREC in the ISF and send a copy to the trial coordinating centre via fax, email or mail).
- Seek an alternative site investigator at the trial site to continue the management and follow-up of participants already randomised.

If this is not possible, and the site must close the site investigator is asked to:

- Inform the steering committee, the trial coordinating centre and their local ethics committee and regulatory bodies of the decisions and reasons, and plans for ongoing management and follow-up of the participants.
- Inform the trial participants of the decision and plans for their management and follow-up.
Trial participants will be followed-up centrally by the trial coordinating centre if necessary.

12. FUNDING

The trial is funded by the National Health and Medical Research Council (NHMRC) project grant 1059094 for five years (2014-2018).

The start-up phase of the trial was funded during 2013 by NHMRC program grant 1013612, University of Sydney bridging support grant 2012-00055, and NHMRC Program grant 5711281.

13. TRIAL ORGANISATION

The AFFINITY trial is coordinated jointly by an established clinical trial team of independent investigators at Sir Charles Gairdner Hospital/University of Western Australia and the George Institute for Global Health in Sydney which has completed the NHMRC-funded VITAmins TO Prevent Stroke (VITATOPS) trial, led by Professor Graeme Hankey; and the Psychosocial Outcomes In StrokE (POISE) study, led by Associate Professor Maree Hackett. Both groups have well-developed systems and procedures for all aspects of the running of large-scale multi-centre clinical trials. Trial management is undertaken at Sir Charles Gairdner Hospital by a team led by Professor Graeme Hankey.

Executive Steering Committee
Associate Professor Maree Hackett, The George Institute for Global Health & The University of Sydney (co-chair)
Professor Graeme J. Hankey, The University of Western Australia & Sir Charles Gairdner Hospital (co-chair)
Professor Osvaldo Almeida, The University of Western Australia
Professor Craig S. Anderson, The George Institute for Global Health
Associate Professor Christopher Etherton-Beer, The 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, The University of Western Australia
Associate Professor Stephen Jan, The George Institute for Global Health
Professor Erik Lundström, Karolinska Institutet, Stockholm.
Professor Gillian Mead, The University of Edinburgh

Acknowledgement is made to the late Professor Veronica Murray, Danderyd Hospital Stockholm for her contributions to the trial as a founding steering committee member.

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.
**Principal Investigator Steering Committee**
All principal investigators at each site

**Data monitoring committee**
**Data Monitoring Committee:**
Professor Robert Hebert, Neuroscience Research Australia
Professor Gregory Carter, University of Newcastle & Calvary Mater Newcastle Hospital
Professor Geoffrey Donnan, The Florey Institute of Neurosciences & Mental Health

**Unblinded Statisticians:**
Associate Professor Qilong Yi, Canadian Blood Services and University of Toronto
Dr Qiang Li, The George Institute for Global Health, Sydney

An independent DMC is established to oversee the safety of participants in the trial. During the period of recruitment, interim analyses of baseline and follow up data is 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 the 180 day assessment) 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 un-blinded interim data.
- Un-blinded analysis of SAEs.
- 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.

**14. AFFINITY SUBSTUDIES**

After stroke, the brain undergoes spontaneous repair and remodelling. However, spontaneous recovery is variable and often incomplete. A better understanding of the mechanisms underlying recovery after stroke promises to advance restorative therapeutics.

Whilst the main AFFINITY trial will determine the overall efficacy of fluoxetine on functional recovery at 6 months after stroke (if it works), it does not address the mechanism of action of fluoxetine (how it works) and optimal patient selection (in whom it works).

A recent systematic review of antidepressants in animal models of ischaemic stroke reported that SSRIs reduced infarct volume by 27.3% (95% CI: 20.7%-33.8%), increased neurogenesis by 2.2 SD (1.3–3.0), and improved neurobehavioral outcome by 51.8% (95% CI: 38.6%–64.9%)[71]. Fluoxetine may also have neuroprotective and other neurotrophic effects.
However, it remains uncertain whether the observed effect of fluoxetine in small trials, such as the FLAME trial [9], if real, may be mediated by augmented neuroprotection, neurogenesis, and neuroplasticity of brain networks, or mood.

The AFFINITY trial substudies aim to assess imaging and blood biomarkers of functional recovery after stroke and response to fluoxetine therapy.

AFFINITY Imaging Biomarker study
A recent meta-analysis of 24 functional magnetic resonance imaging (fMRI) studies of upper limb movement-related brain activity after stroke (n=255 patients) reported that activity in ipsilesional primary motor and medial-premotor cortices after stroke indicated good motor recovery, whereas cerebellar vermis activity signalled poor recovery as compared to healthy controls [72]. Further, a recent review indicated that enhanced recovery can be linked to increased interhemispheric connectivity and increased grey matter volume (cortical thickness) in sensorimotor regions [73-76].

While studies of imaging for prediction of functional recovery after stroke are increasing [77,78] few have analysed the effects of an intervention [73] particularly pharmacological interventions such as fluoxetine. A small clinical trial in 8 patients with stroke reported that fluoxetine was associated with hyperactivation in the ipsilesional primary motor cortex during an active motor task and significantly improved motor skills on the affected side compared with placebo [79,80].

We hypothesize that response to treatment with fluoxetine (vs placebo) will be associated with between group differences in fMRI-based measures of task-related brain activation (specifically ipsilesional primary motor and medial-premotor cortices), enhanced functional connectivity (specifically interhemispheric connectivity) and increased brain volume (cortical thickness), in association with improved motor recovery and functional outcome at 6 months after stroke.

The primary aim of the AFFINITY MR imaging biomarker substudy, led by Professors Andrew Ford, Michael Bynevelt and Leanne Carey, is to determine if random allocation to fluoxetine is associated with

- increased magnitude of activation in the ipsilesional primary motor and medial-premotor cortices, as measured by task-related functional MRI (alternating finger-tapping and rest paradigm) using the blood-oxygen-level dependent (BOLD) contrast fMRI technique, at 6 months after randomization, compared with placebo.

Secondary aims are to determine, at 6 months post-randomisation, if allocation to fluoxetine vs placebo is associated with MRI imaging evidence of:

- increased interhemispheric connectivity of sensorimotor cortices [resting state (RS) fMRI]
- reduced disruption of functional connectivity of depression-related brain networks, including the thalamus (? mood mediation effect of fluoxetine) [RS-fMRI] [81]
- greater volume and thickness of grey matter (cortical thickness) in the ipsilesional primary motor cortex, amygdala, and hippocampus (? neurogenesis) [high resolution structural 3-D T1-weighted MRI]
- greater white matter microstructural integrity and reduced loss of connectivity of white matter tracts [diffusion-weighted MRI (dMRI)] [82]
• reduced volume of the qualifying stroke lesion [T2 fluid attenuation inversion recovery (FLAIR); automated lesion tracing/quantification] [83];

Changes in the above measures, between baseline and 6 months, in each treatment group will also be compared.

Participants recruited to the AFFINITY trial at the SCGH, RMH, John Hunter and Austin hospitals will be invited to undergo the standardised brief MRI protocol (T1WI [cortical thickness], brief dMRI [fractional anisotropy analysis of integrity of white matter tracts], and RS-fMRI [resting state functional connectivity]) immediately after randomization (before the first dose of study drug) and a more detailed MRI protocol (additional task-related fMRI and more detailed dMRI of connectivity) at 6 months after randomization and therapy.

A total of 80 participants (40 per group) will be required to reliably identify or exclude, with 95% power and a two-tailed alpha of 0.05, a difference in magnitude of signal change in motor cortex activation associated with improved motor outcome, relative to usual care, based on effect size in our recent therapy intervention study [84]. In addition, analysis of data specific to modulation of cerebral activation with fluoxetine (Cohen’s D of 1.50, power of 95%, p of 0.05), indicates a minimum sample size of 26. We will recruit 100 participants in total for the AFFINITY fMRI study to allow for a dropout of up to 20% at 6 months.

AFFINITY Blood Biomarker study

Recovery after stroke is likely to be influenced by numerous biomarkers, but single biomarkers could also have important effects. Our preliminary analysis of molecular pathways associated with depression following mass spectrometry proteomic analysis in the START_PrePARE cohort study suggests the involvement of inflammatory, complement and coagulation systems. Further our meta-analysis of biomarkers of stroke-associated depressive illness revealed moderate effects for high cortisol levels and lower serum brain-derived neurotrophic factor (BDNF) levels [85].

Other small studies suggest that polymorphisms in three genes related to neural repair may contribute to variability in functional outcome after stroke; the ApoE ε4 polymorphism, the val66 met BDNF polymorphism, and the R0 mitochondrial DNA haplotype [86-88].

The AFFINITY blood biomarker substudy aims to explore the hypothesis that candidate blood biomarkers, identified through our meta-analyses [89] and PREPARE study [90], and genetic polymorphisms of the ApoE ε4 and val66 met BDNF genes, the R0 mitochondrial DNA haplotype, and other candidate markers of the neuroinflammatory, complement and coagulation systems (e.g. Gadd45b, compound 21, sigma 1 receptor, neurotrophin-3 [NT-3]), are associated independently and significantly with functional outcome after stroke and modulate the effect of fluoxetine on functional recovery. We will derive gene lists associated with good recovery for pathway and gene ontology analyses, and to assess pathways and mechanisms of action associated with treatment.

All participants enrolled in the AFFINITY trial will be invited to consent to provide 15ml of whole blood. 5ml will be placed in an EDTA anticoagulated tube and frozen (-80°C) for later DNA extraction, and 10ml will be placed in a plain serum separator tube and frozen (-80°C) for later separation into 2 separate aliquots (for multiple analyses) [91]. The blood will be stored at -80°C at each investigator site. When 50 samples have been collected, they will be sent as a batch on dry ice to the central laboratory at PathWest, QEII medical centre, Perth for final storage and analysis at the completion of the study (Adj Prof John Beilby, biochemist and Dr. Mark Davis, molecular geneticist). Microarray analyses will be conducted for gene-signature analysis and investigation of mechanisms associated with functional outcome [91].
15. FOCUS TRIAL (UNITED KINGDOM) EFFECTS TRIAL (SWEDEN)

The AFFINITY trial steering committee are collaborating with colleagues in the United Kingdom and Sweden who are concurrently running similar trials. (Fluoxetine or Control under Supervision, FOCUS) at the Department of Geriatric Medicine, Edinburgh and the Neurosciences Trial Unit in Edinburgh, United Kingdom and (Efficacy of fluoxetine—a randomised controlled trial in stroke, EFFECTS) at Karolinska Institutet, Stockholm. Both trials have similar eligibility criteria, treatments, outcome measures and follow-up schedule.

AFFINITY, FOCUS and EFFECTS steering committees 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 committees have registered the review title with the Cochrane Stroke Group. The advantages of carrying out 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 are tailored to that country so that the implication for their health and social services can be deduced.
- The AFFINITY trial is able to explore secondary outcomes which will assist in elucidating possible mechanisms for any effects found.
- There is 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.

16. TRIAL TIMETABLE

Start-up phase
A start-up phase, which aimed to randomise 200 patients in the first year to establish whether the protocol was feasible, was planned. This was to 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 [all of which have been achieved].

Specifically, the start-up phase was to provide realistic estimates of:
1. the range of recruitment rates per hospital and thus the likely number of sites and duration of the main phase. It would also help identify barriers to recruitment which may allow us to increase recruitment rates.
2. the adherence rate, and reasons for non-adherence, which would influence our predicted effect size and power calculations.
3. the follow-up rate.
Sites will be receiving a $1000 payment per participant, payable to the site when all of the following are complete: Randomisation, 28 and 90 day follow-up assessment and submission to the trial coordinating centre by fax or email the participants verified contact details [participant contact sheet] for central follow-up at 6 and 12 months. Invoices will be raised on a quarterly basis, forms are considered complete when they have been submitted and any data queries raised have been answered satisfactorily.

**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>Nov 2011</td>
<td>Apply to ethics committees</td>
</tr>
<tr>
<td>Nov 2011</td>
<td>Database design commences</td>
</tr>
<tr>
<td>Aug 2012</td>
<td>Start-up recruiting sites</td>
</tr>
<tr>
<td>Jan 2013</td>
<td>First participant in trial</td>
</tr>
<tr>
<td>Jul 2013</td>
<td>Six month assessment of first participant in trial</td>
</tr>
<tr>
<td>Jan 2014</td>
<td>Twelve month assessment of first participant in trial</td>
</tr>
<tr>
<td>Dec 2017</td>
<td>Completion of recruitment of 1600 participants</td>
</tr>
<tr>
<td>Dec 2018</td>
<td>Completion of last twelve month assessment</td>
</tr>
<tr>
<td>Apr 2019</td>
<td>Finalisation of database and data lock</td>
</tr>
<tr>
<td>May 2019</td>
<td>Presentation and publication of main results</td>
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</table>

**Main phase**

The main trial will recruit a total of 1600 patients in order to have sufficient statistical power to detect differences in a primary outcome of mRS 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 and (EFFECTS) based in Sweden, 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.

**17. 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. Planned publications will be submitted with an authorship list that states the names of the members of the Executive Steering Committee, Principal Investigator Steering Committee, Un-blinded Statisticians, and Trial Co-ordinating Centre.
18. REFERENCES


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35. Mortensen JK, Larsson H, Johnsen SP, Andersen G. Post Stroke Use of Selective Serotonin Reuptake Inhibitors and Clinical Outcome Among Patients With Ischemic


91. STroke imAging pRevention and Treatment (START) - PrePARE – Prediction and Prevention to Achieve Optimal Recovery Endpoints after stroke, Standalone protocol, V4.0. 26 Aug 2011; LABORATORY PROCEDURE MANUAL VERSION 1.0; 3 November 2011 (Protocol # NTA0902).
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              180 DAY +/- 14 DAYS ASSESSMENT FORM PG 85
              365 DAY +/- 14 DAYS ASSESSMENT FORM PG 101
# APPENDIX 1: NATIONAL INSTITUTE OF HEALTH STROKE SCORE

<table>
<thead>
<tr>
<th>National Institute of Health Stroke Score (NIHSS):</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>1a. Level of Consciousness</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 best only reflex movements to pain)</td>
<td></td>
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<tr>
<td>1b. LOC questions (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 than by than aphasia)</td>
<td></td>
</tr>
<tr>
<td>2: Both incorrect</td>
<td></td>
</tr>
<tr>
<td>1c. LOC commands (ask patient to open/close eyes &amp; form/release a fist)</td>
<td></td>
</tr>
<tr>
<td>0: Obeys both correctly</td>
<td></td>
</tr>
<tr>
<td>1: Obeys one correctly</td>
<td></td>
</tr>
<tr>
<td>2: Both incorrect</td>
<td></td>
</tr>
<tr>
<td>2. Best gaze (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>3. Visual field testing</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>4. Facial Paresis (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>5. Motor function – Arm</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>6. Motor function – Leg</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>7. Limb ataxia (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>8. Sensory (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>9. Best Language (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>10. Dysarthria (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>11. Extinction &amp; inattention (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
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 QUESTIONNAIRE ALGORITHM

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**
  - Are you able to do everything that you were doing right before your stroke, even if slower and not as much?
    - **Yes**
      - Are you completely back to the way you were right before your stroke?
        - **Yes**
          - 0
        - **No**
          - 1
    - **No**
      - 2

- **No**
  - Are you able to walk without help from another person?
    - **Yes**
      - 3
    - **No**
      - 4

Are you bedridden or needing constant supervision?

- **Yes**
  - 5
- **No**
  - 4
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

Fold back this page before administering this questionnaire

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. Diagnoses 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

<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>
PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:  

DATE:  

Over the last 2 weeks, how often have you been bothered by any of the following problems? 

(Use "*" to indicate your answer)

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Some days</th>
<th>Most of the time</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</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 a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead, or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

(add columns: Total)

(Helpful for interpretation of TOTAL, please refer to accompanying scoring card.)

10. If you checked off 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 other people?

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

PHQ-9 is adapted from PRIME MD TODAY, developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr. Spitzer at rls2@columbia.edu. Use of the PHQ-9 may only be made in accordance with the Terms of Use available at http://www.pitzer.com. Copyright ©1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.
APPENDIX 5: TELEPHONE INTERVIEW FOR COGNITIVE STATUS – M

APPENDIX

Telephone Interview for Cognitive Status (TICS-M)

Score ‘1’ for each correct answer and ‘0’ if incorrect

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

Registration/Free Recall
4. I’m going to read you a list of 10 words, Cabin
   Please listen carefully and try to remember Pipe
   them. When I am done, tell me as many as Elephant
   you can in any order. Ready? Chest
   Silk
   Theatre
   Now, tell me all the words you can remember Watch
   Whip
   Pillow
   Giant

Attention/Calculation
5. Please take 7 away from 100 93
   Now continue to take 7 away from what 86
   you have left over until I ask you to stop. 79
   72
   65
   No mistakes

Comprehension, Semantic and Recent Memory
6. Please count backwards from 20 to 1

Language/Repetition
7. What do people usually use to cut paper? Scissors
8. What is the prickly green plant found in the desert? Cactus
9. Who is the reigning monarch now? E, QE, QE2
10. Who is the Prime Minister now? Correct surname
11. What is the opposite of east? West

Delayed Recall
12. Please say this ‘Methodist Episcopal’ Exactly right
13. Please repeat the list of 10 words I read earlier
   Cabin
   Pipe
   Elephant
   Chest
   Silk
   Theatre
   Watch
   Whip
   Pillow
   Giant
   □ maximum of 39
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.

<table>
<thead>
<tr>
<th>3. In the past week, how often did you...</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.

<table>
<thead>
<tr>
<th>4. In the past week, how difficult was it to...</th>
<th>Not at all difficult</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.

5. In the past 2 weeks, how difficult was it to...

<table>
<thead>
<tr>
<th>Activity</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. 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. 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. Bathe yourself?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Clip your toenails?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. 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. 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. 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. 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. Go shopping?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>j. 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.

6. In the past 2 weeks, how difficult was it to...

<table>
<thead>
<tr>
<th>Activity</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. 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. 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. 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. 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. Walk one block?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Walk fast?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. 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. 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. 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?</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
- 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 = □
APPENDIX 9: TRIAL MATERIALS

AFFINITY TRIAL RANDOMISATION & BASELINE FORM

Please use a black pen & BLOCK PRINT IN CAPITALS
Please complete this baseline form on the day of randomisation, between 2 and 15 days post stroke
Randomisation MUST be done via the AFFINITY website www.affinitytrial.org
You MUST complete this form before logging on to the randomisation system

Date of Assessment: (dd/mm/yyyy) □□/□□/□□□□□

AFFINITY number □□□□ Patient Initials □□ Randomising person: ______________________________

Collaborating centre: ___________________________ Consultant _______________________________

1. Is the Patient Eligible? Yes □ No □

Inclusion criteria (check all criteria are met and all boxes ticked)
☐ Men and Women aged >18 years
☐ 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 (intracerebral and/or subarachnoid) 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 produce a modified Rankin Scale (mRS) score of ≥ 1 and to warrant treatment from the perspective of patient or carer(s).

Exclusion criteria (check no criteria are met and no boxes ticked)
☐ History of epilepsy seizures
☐ History of bipolar disorder
☐ History of drug overdose or attempted suicide
☐ Ongoing treatment with any selective serotonin reuptake inhibitor (SSRI)
☐ Allergy or contra indication to fluoxetine including
  ➢ hepatic impairment (serum alanine aminotransferase [ALT] >120 UI),
  ➢ renal impairment (creatinine > 190 micromol/L or eGFR < 30ml/min/1.73m²),
  ➢ hypotension (sodium < 125 mmol/l) despite treatment of the cause and confirmed on repeat testing,
☐ Use of medications that may interact seriously with fluoxetine
  ➢ Proposed use of a monoamine oxidase inhibitor (MAOI), or of use of a MAOI within 14 days prior to randomisation
  ➢ Current treatment with an antipsychotic drug (neuroleptic), pimozide, tamsulosin, or tramadol unless the patient, doctor and if possible prescribng doctor, believe it is appropriate to discontinue use
☐ Not available for follow up over the next 365 days e.g. no fixed home address
☐ Life-threatening illness (e.g. advanced cancer) that is likely to reduce 365 day survival
☐ Pregnant, breast-feeding or of child-bearing potential and not using contraception
☐ Enrolled in another interventional clinical research trial involving an investigational product (medicine) or device.

2. Consent

Has written consent been obtained from the patient or their legal representative? Yes □ No □

Given by: (please circle): Patient or Person Responsible or Waiver acknowledgement

Obtained by: ________________________________

Date Obtained: (dd/mm/yyyy) □□/□□/□□□□□

AFFINITY Randomisation Form Version 6, 18th November 2015
3. Patient Demographics

Gender: Male ☐ Female ☐

Date of Birth (dd/mm/yyyy): ☐/☐/☐☐☐☐

Ethnicity: Caucasian ☐ African ☐
Asian ☐ Other ☐ Please specify ____________
Aboriginal/Torres Strait Islander ☐

Marital Status: Married ☐ Single ☐
Widowed ☐ Separated/Divorced ☐
Partner ☐ Other ☐ Please specify ____________

Living Arrangements before your stroke: Home Alone ☐ Permanent care facility ☐
Living at home with someone else ☐ Other ☐ Please specify ____________

Employment: Full time ☐ Part time ☐
Voluntary ☐ Retired ☐
Unemployed or Disabled ☐ Other ☐ Please specify ____________

Is the patient currently an inpatient? Yes ☐ No ☐

4. Functional status immediately before this stroke: (please circle)

0 No symptoms

1 Slight disability; unable to perform all previous activities but able to look after own affairs without assistance

2 Moderate disability; requires some help, but may be able to walk without assistance

3 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

4 Severe disability; bedridden, incontinent and requires constant nursing care and attention

5. Details of Stroke

Date of stroke: (dd/mm/yyyy) ☐/☐/☐☐☐☐
6. Neurological Impairments (functional deficits):

<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 best 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 than by 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. Always both correctly</td>
<td></td>
</tr>
<tr>
<td>1. Always 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 palsy 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</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 paralyses (flattened nasolabial fold, asymmetry of smiling)</td>
<td></td>
</tr>
<tr>
<td>2. Partial paralyses (total or near total paralyses of lower face)</td>
<td></td>
</tr>
<tr>
<td>3. Complete paralyses 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>5b. Motor function – Leg</strong></td>
<td></td>
</tr>
<tr>
<td>0. Normal (holds leg in 90° 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. Unstable (joint fused or limb amputated) (do not add score)</td>
<td></td>
</tr>
<tr>
<td><strong>7. Limb ataxia</strong> (fingernose, festination 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. M.e (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. Nearly unrecognizable or unable to speak</td>
<td></td>
</tr>
<tr>
<td>U. Untestable (muttered 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. Irregular extinction to bilateral stimulation in one of the sensory modalities</td>
<td></td>
</tr>
<tr>
<td>2. Severe extinction or loss of attention to more than one modality</td>
<td></td>
</tr>
</tbody>
</table>

Total Score
7. Primary Outcome: Simplified Modified Rankin Scale questionnaire (Circle each response on pathway & final score)

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**
  - Are you able to do everything you were doing right before your stroke, even if slower and not as much?
    - **YES**
      - Are you completely back to the way you were right before your stroke?
        - **YES**
          - 0
        - **NO**
          - 1
    - **NO**
      - 2
- **NO**
  - Are you able to walk without help from another person?
    - **YES**
      - Are you bedridden or needing constant supervision?
        - **YES**
          - 5
        - **NO**
          - 4
    - **NO**
      - 3

Score

8. Type of Stroke (Ischaemic or Haemorrhagic)

Does brain scan show recent bleeding? Yes ☐ No ☐ (If no please answer 8a and 8b.)

If yes, is the bleeding likely to be due to haemorrhagic transformation of an infarct? Yes ☐ No ☐

If yes, please answer 8a and 8b

If no, please specify type of haemorrhage? i) Intracerebral haemorrhage ☐ (please answer 8a and 8c.)
ii) Subarachnoid haemorrhage ☐ (please answer 8c.)

8a. What was the clinical syndrome of the qualifying stroke? (please tick most appropriate)

i. Total Anterior Circulation Syndrome (TACS) ☐
ii. Partial Anterior Circulation Syndrome (PACS) ☐
iii. Lacunar Syndrome (LACS) ☐
iv. Posterior Circulation Syndrome (POCS) ☐
v. Uncertain ☐
8b. What is the most likely cause of the ischaemic stroke? (please tick most likely)
   i. Large artery disease (cortical stroke (TACS/PACS + arterial stenosis >50% with no other cause))
   ii. Small vessel disease (LACS without arterial stenosis or cardiac source)
   iii. Embolism from the heart (e.g. atrial fibrillation, cardiomyopathy, endocarditis)
   iv. Another cause (e.g. dissection, illicit drugs)
   v. Unknown or uncertain cause (no cause identified or more than one of above)

8c. What is the likely cause of the haemorrhagic stroke? (please tick most likely)
   i. Hypertension
   ii. Amyloid angiopathy
   iii. Antithrombotic therapy
   iv. Arteriovenous malformation
   v. Aneurysm
   vi. Other,
   vii. Unknown or uncertain

9. Depression
   i. Previous depression requiring treatment? (Treatment can be Drugs/Counselling/other) Yes ☐ No ☐
   ii. Current depression requiring treatment? (Treatment can be Drugs/Counselling/other) Yes ☐ No ☐

10. PHQ-9 (please circle) Over the past 2 weeks, have you been bothered by:

    Scoring - 0: not at all; 1: several days; 2: more than half the days; 3: nearly every day

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
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<td>2</td>
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<td>3</td>
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<td>7</td>
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TOTAL ☐ if score ≥ 15/27 notify GP: Yes ☐ No ☐ NA ☐
Not able to complete ☐

10. If you have checked off any problems in the PHQ-9 above, how difficult have these problems made it for you to do your work, take care of things at home, or to get along with other people?
    Not difficult at all ☐
    Somewhat difficult ☐
    Very difficult ☐
    Extremely difficult ☐
11. Co-morbidities
i. History of Diabetes  
   Yes ☐ No ☐ Unknown ☐
ii. Previous Coronary Heart Disease (ie definite angina, MI, CABG, coronary stenting)  
   Yes ☐ No ☐ Unknown ☐
iii. Previous ischaemic stroke/TIA or stroke of uncertain pathology (before this event)  
   Yes ☐ No ☐ Unknown ☐
iv. Previous Intracranial bleeding (including prior haemorrhagic stroke or subdural)  
   Yes ☐ No ☐ Unknown ☐
v. Past history of upper gastrointestinal bleeding  
   Yes ☐ No ☐ Unknown ☐
vi. Past history of Hyponatraemia (Sodium <125mmol/L)  
   Yes ☐ No ☐ Unknown ☐
vii. Bone Fractures  
   Yes ☐ No ☐ Unknown ☐

12. Was the patient thrombolysed for this event?  
   Yes ☐ No ☐

13. Current Medications
Please list generic names of all medications being taken at the time of randomisation

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14. Laboratory Testing
14a. ALT
Result: ☐ U/L  
   (if >120 U/L, please treat, repeat test and reassess before randomising)

14b. Creatinine
Result: ☐ micromol/L  
   (if >180 micromol/L please treat, repeat test and reassess before randomising)

14c. eGFR
Result: ☐  
   (if < 30, please treat, repeat test and reassess randomisation)

14d. Blood sodium
Result: ☐ mmol/L  
   (if <125 mmol/L, please treat, repeat and reassess before randomising)
15. Randomisation

To randomise this patient please log on to the AFFINITY trial website: www.affinitytrial.org

Please record the date of randomisation, patient ID and allocated treatment numbers below

Date of randomisation (dd/mm/yyyy) ☐☐/☐☐/☐☐/☐☐/☐☐/☐☐/☐☐/☐☐/☐☐/☐☐/

AFFINITY trial patient ID number: ☐☐☐☐

Allocated treatment number: ☐☐☐☐

Medication Start Date (dd/mm/yyyy) ☐☐/☐☐/☐☐/☐☐/☐☐/☐☐/☐☐/☐☐/☐☐/☐☐/

Please write a prescription for a 6 month supply of AFFINITY trial medication.

Rx ☐☐☐☐ trial medication (Fluoxetine 20mg or Placebo)
AFFINITY Treatment No.
Dose: One capsule daily
Route: Oral or NG/PEG (if cannot swallow)
Quantity: 6 month supply
Name of prescriber: Signature: Date:

Please make a follow-up appointment for the patient for 28 days from the randomisation date.

Please file the original copy of this randomisation form in the patient’s AFFINITY folder and place a copy of the signed PISC in the patient’s medical records

End of Baseline Assessment (thank you)
Assessment Date: (dd/mm/yyyy) [ ]/ [ ]/[ ]/ [ ]/ [ ]/ [ ]/ Collaborating centre: ________________

AFFINITY number □ □ □ □ □ □ □ □ □ □ □ □ □ Patient Initials □ □ Person completing this form: ________________

Main source of the data: (please circle) Patient or Proxy or Medical Records or Other

1. Type of follow-up: (please circle)
   Clinic □ Hospital □ Telephone □ Other (please list) ________________

2. Survival: is the patient alive at scheduled date of assessment?
   Yes □ No □
   (If deceased, please complete a serious adverse event form.)

3. Current Living Arrangements: Home alone □ Living at home with someone else □ Permanent care facility □
   Rehab □ Other □ Please Specify ________________

4. Clarification of the final diagnosis and cause of the qualifying stroke:
   4a. Was the final diagnosis in this patient a definite stroke? Yes □ No □
       (a normal brain scan is compatible with a diagnosis of ischaemic stroke)
       If No, please specify the final diagnosis: ________________

       If Yes, what type of stroke was this?
       i. Ischaemic □ (please answer Q4c and d.)
       ii. Haemorrhagic □ (please answer Q4b.)

   4b. What type of haemorrhagic stroke?
       i. Intracerebral haemorrhage □ (please answer Q4c and e.)
       ii. Subarachnoid haemorrhage □ (please answer Q4e.)

   4c. What was the clinical syndrome of the qualifying stroke?
       i. Total Anterior Circulation Syndrome (TACS) □
       ii. Partial Anterior Circulation Syndrome (PACS) □
       iii. Lacunar Syndrome (LACS) □
       iv. Posterior Circulation Syndrome (POCS) □
       v. Uncertain □

   4d. For patients with ischaemic stroke, what was the cause?
       i. Large artery disease (cortical stroke (TACS/PACS + carotid atheroma >50% with no other cause) □
       ii. Small vessel disease (LACS without carotid atheroma or cardiac source) □
       iii. Embolism from the heart (e.g. Atrial Fibrillation, prosthetic valve, endocarditis) □
       iv. Another cause (e.g. dissection, illicit drugs) □
       v. Unknown or uncertain cause (no cause identified or more than one of above) □

   4e. What is the likely cause of the haemorrhagic stroke? (please tick most likely)
       i. Hypertension □
       ii. Amyloid angiopathy □
       iii. Antithrombotic therapy □
       iv. Arteriovenous malformation □
       v. Aneurysm □
       vi. Other □
       vii. Unknown or uncertain □
5. Current Medications: Please list all the medications the patient is currently taking.

<table>
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<tr>
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<th>Stop Date</th>
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6. Medication Compliance:
   
   a. On average, since last follow up how many times per week was the AFFINITY trial medication taken (patient report)?
      
      (0) times per week
      (1-2) times per week
      (3-4) times per week
      (5-6) times per week
      (7) times per week
   
   b. How many capsules are remaining in the bottle? __________
   
   c. Did patient stop the trial medication at all since the last follow up?
      
      Yes, temporarily
      Yes, permanently
      No
      
      Date Stopped (dd/mm/yyyy): __________
      Date Re-started (dd/mm/yyyy): __________

    Reason:

7. Serious Adverse Events and/or Secondary Outcome Events since randomisation:

   New stroke, ischaemic or haemorrhagic [not the qualifying stroke leading to enrolment] Yes ☐ No ☐
   Acute coronary syndrome [MI confirmed on ECG and/or raised serum Troponin] Yes ☐ No ☐
   Upper gastrointestinal bleed requiring blood transfusion and/or endoscopy Yes ☐ No ☐
   Other major bleed (i.e. not upper GI or intracerebral) Yes ☐ No ☐
     - Requiring blood transfusion or procedural intervention
   Fall Yes ☐ No ☐
   New fracture [confirmed on X Ray] Yes ☐ No ☐
   Epileptic seizure [focal or generalised] Yes ☐ No ☐
   Symptomatic hypoglycaemia [blood sugar < 3mmol/l] Yes ☐ No ☐
   Symptomatic hyperglycaemia [blood sugar >22mmol/l] Yes ☐ No ☐
   New hyponatraemia [Na < 125mmol/l] Yes ☐ No ☐
   Attempted suicide/self-harm Yes ☐ No ☐
   Other SAE Yes ☐ No ☐
Please complete a “Serious Adverse Event and Secondary Outcome Event” form immediately if a patient has answered "Yes" to any of the above events that:

- are unexpected reactions to the AFFINITY trial medication (i.e. not consistent with the product information)
- result in death;
- are life threatening (i.e. the participant was at risk of death due to the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- require hospitalisation or prolongation of existing hospitalisation;
- result in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- results in a secondary outcome event for the AFFINITY Trial (new stroke, ischaemic or haemorrhagic [not the qualifying stroke leading to enrolment], acute coronary syndrome [MI confirmed on ECG and/or raised serum Troponin], upper gastrointestinal bleed requiring blood transfusion and/or endoscopy, other major bleed (i.e. not upper GI or intracerebral) requiring blood transfusion or procedural intervention, new fracture [confirmed on X Ray], epileptic seizure [focal or generalised], new hyponatraemia [Na<125mmol/l] or attempted suicide/self-harm).

8. Pregnancy: Yes ☐ No ☐ N/A ☐

Please complete a separate 'pregnancy notification form'.

Primary Outcome

9. Simplified Modified Rankin Scale questionnaire: (Circle each response on pathway & final score)

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 ☐ N/A ☐

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

Yes ☐ No ☐

2

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

Yes ☐ No ☐

3

Are you able to walk without help from another person?

Yes ☐ No ☐

4

Are you bedridden or needing constant supervision?

Yes ☐ No ☐

5

Score ☐
Secondary Outcomes

10. New clinical diagnosis of depression:
   a. Has the patient been diagnosed with depression since randomisation?  Yes ☐ No ☐
   b. Has the patient been treated for depression since randomisation? (non-pharmacological) Yes ☐ No ☐
   c. Has the patient been prescribed an antidepressant drug for treatment of depression since randomisation? Yes ☐ No ☐
      If yes, to Q10c please ensure you have documented this on the current medication list.

11. PHQ-9 (please circle) Over the past 2 weeks, have you been bothered by:

Scoring - 0 not at all; 1: several days; 2: more than half the days; 3: nearly every day

<table>
<thead>
<tr>
<th></th>
<th>Little interest or pleasure in doing things?</th>
<th>Feeling down, depressed, or hopeless?</th>
<th>Trouble falling or staying asleep, or sleeping too much?</th>
<th>Feeling tired or having little energy?</th>
<th>Poor appetite or overeating?</th>
<th>Feeling bad about yourself- or that you are a failure or have let yourself or your family down?</th>
<th>Trouble concentrating on things, such as reading the newspaper or watching television?</th>
<th>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 a lot more than usual?</th>
<th>Thoughts that you would be better off dead, or of hurting yourself in some way?</th>
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</table>

TOTAL ☐ If score ≥ 15/27 notify GP: Yes ☐ No ☐ NA ☐ Not able to complete ☐

10. If you have checked off any problems above, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

   Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult ☐

Please enter this information onto the corresponding form via the AFFINITY website www.affinitytrial.org

End of 28 Day Assessment (thank you)
**AFFINITY trial 90 DAY +/- 14 days ASSESSMENT FORM**

Please use a black pen & BLOCK PRINT IN CAPITALS

### Assessment Date:
(dd/mm/yyyy) [ ] [ ] [ ] [ ] [ ]

Collaborating centre: ____________________________

### AFFINITY number: [ ] [ ] [ ] [ ]

Patient Initials: [ ]

Person completing this form: [ ]

### Main source of the data (please circle):
- Patient  [ ]
- Proxy  [ ]
- Medical Records  [ ]
- Other (please list) [ ]

1. **Type of follow-up: (please circle):**
   - Clinic  [ ]
   - Hospital  [ ]
   - Telephone  [ ]
   - Other (please list)  [ ]

2. **Survival: Is the patient alive at scheduled date of assessment?**
   - Yes  [ ]
   - No [ ]

   (If deceased, please complete a serious adverse event form.)

3. **Current Living Arrangements:***
   - Home alone  [ ]
   - Living at home with someone else  [ ]
   - Permanent care facility  [ ]
   - Rehab  [ ]
   - Other  [ ]
   - Please Specify: ____________________________

4. **Current Medications:**

   Please list all the medications the patient is currently taking.

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<tr>
<th>Generic Name</th>
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5. **Medication Compliance**

   a. On average, since last follow up how many times per week was the AFFINITY trial medication taken (patient report)?
      - (0) times per week
      - (1-2) times per week
      - (3-4) times per week
      - (5-6) times per week
      - (7) times per week

   b. How many capsules are remaining in the bottle? ____________________________

   c. Did patient stop the trial medication at all since the last follow up?
      - Yes, temporarily  [ ]
      - Yes, permanently  [ ]
      - No  [ ]

      NA – permanently ceased reported on previous follow-up  [ ]

      Date Stopped  (dd/mm/yyyy) [ ] [ ] [ ] [ ] [ ] [ ]

      Date Re-started (dd/mm/yyyy) [ ] [ ] [ ] [ ] [ ] [ ]

      Number of days off AFFINITY medication: ____________________________

      Reason: ____________________________
6. **Serious Adverse Events and/or Secondary Outcome Events since 28 day follow-up:**

<table>
<thead>
<tr>
<th>Event</th>
<th>Yes</th>
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Please complete a “Serious Adverse Event and Secondary Outcome Event” Form immediately if a patient has answered “Yes” to any of the above events that:

- are unexpected reactions to the AFFINITY trial medication (i.e. not consistent with the product information)
- result in death;
- are life threatening (i.e. the participant was at risk of death due to the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
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7. **Pregnancy:** Yes ☐ No ☐ N/A ☐

Please complete a separate ‘pregnancy notification form’.
Primary Outcome

8. Simplified Modified Rankin Scale questionnaire *(Circle each response on pathway & final score)*

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**
  - Are you able to do everything you were doing right before your stroke, even if slower and not as much?
    - **YES**
      - Are you completely back to the way you were right before your stroke?
        - **YES**
          - 0
        - **NO**
          - 1
    - **NO**
      - 2

- **NO**
  - Are you able to walk without help from another person?
    - **YES**
      - Are you bedridden or needing constant supervision?
        - **YES**
          - 4
        - **NO**
          - 5
    - **NO**
      - 3

Score [ ]

Secondary

Outcomes

9. New clinical diagnosis of depression
   a. Has the patient been diagnosed with depression since the last assessment?  
      Yes [ ]  No [ ]
   b. Has the patient been treated for depression since the last assessment? (non-pharmacological)  
      Yes [ ]  No [ ]
   c. Has the patient been prescribed an antidepressant drug for treatment of depression since the last assessment?  
      Yes [ ]  No [ ]

If yes, to Q6c please ensure you have documented this on the current medication list.
10. PHQ-9 (please circle) Over the past 2 weeks, have you been bothered by:

Scoring - 0: not at all; 1: several days; 2: more than half the days; 3: nearly every day

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TOTAL □ If score ≥ 15/27 notify GP: Yes □ No □ NA □ Not able to complete □

10. If you have checked off 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 other people?

Not difficult at all □ Somewhat difficult □ Very difficult □ Extremely difficult □

Please notify the participant that they will be followed-up centrally by the trial coordinating centre who will be in contact with them shortly via mail.

Please scan and email (affinitytrial@health.wa.gov.au or fax 08 6151 1028) the AFFINITY trial patient contact information sheet to the trial coordinating centre.

Please enter this information onto the corresponding form via the AFFINITY website www.affinitytrial.org

Please review/update the patients Hospital Admission and GP/Specialist diary and add any changes to the online form

End of 90 Day Assessment (thank you)
AFFINITY trial 180 DAY +/- 14 days ASSESSMENT FORM

Please use a black pen & BLOCK PRINT IN CAPITALS

Assessment Date: (dd/mm/yyyy) □□/□□/□□/□□/□□□□ Collaborating centre: □□□□□□□□

AFFINITY number □□□□□□□□ Patient Initials □□□□ Person completing this form: □□□□□□□□

Main source of the data (please circle): Patient or Proxy or Medical Records or Other

1. Type of follow-up: (please circle)
   Clinic □□□□ Hospital □□□□ Telephone □□□□ Other (please list) □□□□□□□□

2. Survival: Is the patient alive at scheduled date of assessment? Yes □ No □
   (If deceased, please complete a serious adverse event form)

3. Current Living Arrangements: Home alone □□□□ Living at home with someone else □□□□
   Permanent care facility □□□□ Rehab □□□□ Other □□□□ Please Specify □□□□□□□□

4. Current Medications: Please list all the medications the patient is currently taking.

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<td>9.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
<td></td>
<td>10.</td>
<td></td>
<td></td>
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<tr>
<td>4.</td>
<td></td>
<td></td>
<td>11.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td></td>
<td>12.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td></td>
<td></td>
<td>13.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td></td>
<td></td>
<td>14.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. Medication Compliance
   a. On average, since last follow up how many times per week was the AFFINITY trial medication taken (patient report)?
      (0) times per week □□□□□□ (1-2) times per week □□□□□□ (3-4) times per week □□□□□□ (5-6) times per week □□□□□□ (7) times per week □□□□□□
   b. How many capsules are remaining in the bottle? □□□□□□□□
   c. Did patient stop the trial medication at all since the last follow up?
      Yes, temporarily □□□□□□□□ If Yes, specify dates and reason:
      Yes, permanently □□□□□□□□ If Yes, specify dates and reason:
      No □□□□□□□□
      NA- permanently ceased reported on previous follow-up □□□□□□□□

Date Stopped □□/□□/□□/□□/□□□□
Date Re-started □□/□□/□□/□□/□□□□

Reason: □□□□□□□□□□
Number of days off AFFINITY medication: □□□□□□□□

AFFINITY 180 Day Assessment Form Version 6, 18th November 2015
6. End of AFFINITY Trial Medication

Date completed AFFINITY trial medication (please enter the date of the last dose taken)

7. Serious Adverse Events and/or Secondary Outcome Events since 90 day follow-up:

<table>
<thead>
<tr>
<th>Event</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>New stroke, ischaemic or haemorrhagic (not the qualifying stroke leading to enrolment)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Acute coronary syndrome [MI confirmed on ECG and/or raised serum Troponin]</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Upper gastrointestinal bleed requiring blood transfusion and/or endoscopy</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other major bleed (i.e. not upper GI or intracerebral) - Requiring blood transfusion or procedural intervention</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Fall</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>New fracture [confirmed on X Ray]</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Epileptic seizure [focal or generalised]</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Symptomatic hypoglycaemia [blood sugar &lt; 3mmol/l]</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Symptomatic hyperglycaemia [blood sugar &gt;22mmol/l]</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>New hyponatraemia [Na &lt; 125mmol/l]</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Attempted suicide/self-harm</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Other SAE</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

Please complete a “Serious Adverse Event and Secondary Outcome Event” Form immediately if a patient has answered “Yes” to any of the above events that:
- are unexpected reactions to the AFFINITY trial medication (i.e. not consistent with the product information)
- result in death;
- are life threatening (i.e. the participant was at risk of death due to the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- require hospitalisation or prolongation of existing hospitalisation;
- result in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- results in a secondary outcome event for the AFFINITY Trial (new stroke, ischaemic or haemorrhagic [not the qualifying stroke leading to enrolment], acute coronary syndrome [MI confirmed on ECG and/or raised serum Troponin], upper gastrointestinal bleed requiring blood transfusion and/or endoscopy, other major bleed [i.e. not upper GI or intracerebral] requiring blood transfusion or procedural intervention, new fracture [confirmed on X Ray], epileptic seizure [focal or generalised], new hyponatraemia (Na<125mmol/l) or attempted suicide/self-harm).

8. Pregnancy: Yes ☐ No ☐ N/A ☐

Please complete a separate ‘pregnancy notification form’.

9. Health care Utilisation:

   a. Hospitalisation days since enrolment (not including hospitalisation for the initial/qualifying stroke)
   
   b. Days spent in care at home since enrolment?
   
   c. Formal carers – total number of visits per week?
Primary Outcome

10. Simplified Modified Rankin Scale questionnaire (Circle each response on pathway & final score)

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**
  - Are you able to do everything 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**
      - Score

- **NO**
  - Are you able to walk without help from another person?
    - **YES**
    - **NO**
    - Are you bedridden or needing constant supervision?
      - **NO**
      - **YES**
      - Score
Secondary Outcomes

11. New clinical diagnosis of depression
   a. Has the patient been diagnosed with depression since the last assessment? [Yes □ No □]
   b. Has the patient been treated for depression since the last assessment? (non-pharmacological) [Yes □ No □]
   c. Has the patient been prescribed an antidepressant drug for treatment of depression since the last assessment? [Yes □ No □]

   If yes, to Q11c please ensure you have documented this on the current medication list.

12. PHQ-9 (please circle) Over the past 2 weeks, have you been bothered by:

   Scoring - 0: not at all; 1: several days; 2: more than half the days; 3: nearly every day

<table>
<thead>
<tr>
<th>Question</th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things?</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless?</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much?</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy?</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating?</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself- or that you are a failure or have let</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>yourself or your family down?</td>
<td></td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>watching television?</td>
<td></td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>Or the opposite – being so fidgety or restless that you have been</td>
<td></td>
</tr>
<tr>
<td>moving around a lot more than usual?</td>
<td></td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead, or of hurting yourself</td>
<td>0 1 2 3</td>
</tr>
<tr>
<td>in some way?</td>
<td></td>
</tr>
</tbody>
</table>

   TOTAL □ If score ≥ 15/27 notify GP: [Yes □ No □ NA □]

   Not able to complete □

10. If you checked off 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 other people?

   Not difficult at all □
   Somewhat difficult □
   Very difficult □
   Extremely difficult □
13. Cognition (TICSm)

Score ‘1’ for each correct answer and ‘0’ if incorrect in the boxes provided

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

Registration
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? Cabin ☐ Pipe ☐ Elephant ☐ Chest ☐ Silk ☐
   Now tell me all the words you can remember. Theatre ☐ Watch ☐ Whip ☐ Pillow ☐ Giant ☐

Attention/Calculation
5. Please take away 7 from 100 93 ☐
   Now continue to take 7 away from what you have left over until I ask you to stop. 86 ☐ 79 ☐ 72 ☐ 65 ☐
6. Please count backwards from 20 to 1 no mistakes ☐

Comprehension, Semantic & Recent Memory
7. What do people usually use to cut paper? Scissors ☐
8. What is the prickly green plant found in the desert Cactus ☐
9. Who is the reigning monarch now? E, QE, QE2 ☐
10. Who is the Prime Minister now? Correct surname ☐
11. What is the opposite of east? West ☐

Language/Repetition
12. Please say this ‘Methodist Episcopal’ Exactly right ☐

Delayed Recall
13. Please repeat the list of 10 words I read earlier Cabin ☐ Pipe ☐ Elephant ☐ Chest ☐ Silk ☐
    Theatre ☐ Watch ☐ Whip ☐ Pillow ☐ Giant ☐

Total Score 39/39
14. Fatigue (Vitality Domain of SF 36) (please circle)

The following questions are about how you feel and about how things have been with you in the past four weeks. As I read statement, please give me the one answer that comes closest to the way you have been feeling.

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. How much of the time during the past four weeks did you feel full of life?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. How much of the time during the past four weeks did you have a lot of energy?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. How much of the time during the past four weeks did you feel worn out?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. How much of the time during the past four weeks did you feel tired?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
15. Health-related quality of life (EQ-5D-5L):
Under each heading, please tick the ONE box that best describes your health TODAY

Mobility
1. I have no problems with walking around
2. I have slight problems with walking around
3. I have moderate problems with walking around
4. I have severe problems with walking around
5. I am unable to walk around

Personal Care
6. I have no problems with washing or dressing myself
7. I have slight problems with washing or dressing myself
8. I have moderate problems with washing or dressing myself
9. I have severe problems with washing or dressing myself
10. I am unable to wash or dress myself

Usual Activities (e.g. work, study, housework, family or leisure activities)
11. I have no problems doing my usual activities
12. I have slight problems doing my usual activities
13. I have moderate problems doing my usual activities
14. I have severe problems doing my usual activities
15. I am unable to do my usual activities

Pain / Discomfort
16. I have no pain or discomfort
17. I have slight pain or discomfort
18. I have moderate pain or discomfort
19. I have severe pain or discomfort
20. I have extreme pain or discomfort

Anxiety / Depression
21. I am not anxious or depressed
22. I am slightly anxious or depressed
23. I am moderately anxious or depressed
24. I am severely anxious or depressed
25. I am extremely anxious or depressed

• 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 on the next page to indicate how your health is TODAY.
• Now, please write the number you marked
  on the scale in the box.
26. YOUR HEALTH TODAY =  

The best health you can imagine

The worst health you can imagine
16. Overall health status (SIS) (please circle)

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>

Note: If you have no affected, or weaker, side then score your dominant side i.e. your right side if you are right handed, or your left side if you are left handed.

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.

<table>
<thead>
<tr>
<th>3. In the past week, how often did you...</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.

<table>
<thead>
<tr>
<th>4. In the past week, 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>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Say the name of someone 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 dialling?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: If you do not do any or all of these code them as **Extremely Difficult**.

Item f. If you do not call but are handed the phone this is OK.

Item g. If you cannot hold a phone book, if you can read it this is OK. This item addresses whether you are able to initiate a phone call, look up the number, and dial this number correctly.
The following questions ask about activities you might do during a typical day.

<table>
<thead>
<tr>
<th>5. 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. 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. 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. Bathe yourself?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Clip your toenails?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. 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. 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. 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. Do light household tasks/chores (e.g. dust, make a bed, take out the garbage, do the dishes)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>i. Go shopping?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>j. Do heavy household chores (vacuum, laundry or yard work)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: If you do not do any or all of the activities listed, code them as Cannot do at all.
Item a. If you are on pureed food, even if you feel you could cut the food, code as Cannot do at all.
Item c. Bathing oneself does not include getting into the bath.
Item e. This question is associated with movement. Does the person have the physical ability to get to the bathroom quickly enough?
Item f. Losing a little urine/dribbling is considered an accident. If you have a catheter, code as Cannot do at all.
Item g. Constipation is not counted here, person has to have an accident.
Item i. “Shopping” means any type of shopping and does not include driving.

The following questions are about your mobility at home and in the community.

<table>
<thead>
<tr>
<th>6. 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. 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. 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. 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. 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. Walk one block?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Walk fast?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. 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. 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. Get in and out of the car?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: If you have not done any of the items in the past two weeks code as Cannot do at all.
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 5 cent piece?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

**Notes:** If you have no affected, or weaker, side then score your dominant side i.e. your right side if you are right handed, or your left side if you are left handed.

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. In 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>

**Notes:** If you don’t do any of the specific items, and has never done, code as None of the time.
9. 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

Please notify the participant that we will be in contact with them 6 months from now (i.e. 12 months from date of Randomisation)

Please enter this information onto the corresponding form via the AFFINITY website www.affinitytrial.org

End of 180 Day Assessment (thank you)
AFFINITY trial 365 DAY +/- 14 days ASSESSMENT FORM

Please use a black pen & BLOCK PRINT IN CAPITALS

Assessment Date: (dd/mm/yyyy) [ ] / [ ] / [ ] / [ ] / [ ] / [ ] / [ ] / [ ] / [ ] / [ ] Collaborating centre: [___________]

AFFINITY number [ ] [ ] [ ] Patient Initials [ ] [ ] Person completing this form: [___________]

Main source of the data (please circle): Patient or Proxy or Medical Records or Other

1. Type of follow-up: (please circle)
   - Clinic
   - Hospital
   - Telephone
   - Other (please list) [___________]

2. Survival: Is the patient alive at scheduled date of assessment? [Yes [ ] No [ ]]
   (If deceased, please complete a serious adverse event form.)

3. Current Living Arrangements: Home alone [ ] Living at home with someone else [ ] Permanent care facility [ ]
   - Rehab [ ]
   - Other [ ] Please Specify [___________]

4. Current Medications: Please list all the medications the patient is currently taking.

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Start Date</th>
<th>Stop Date</th>
<th>Generic Name</th>
<th>Start Date</th>
<th>Stop Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>2.</td>
<td>3.</td>
<td>4.</td>
<td>5.</td>
<td>6.</td>
</tr>
<tr>
<td>7.</td>
<td>8.</td>
<td>9.</td>
<td>10.</td>
<td>11.</td>
<td>12.</td>
</tr>
<tr>
<td>18.</td>
<td>19.</td>
<td>20.</td>
<td>21.</td>
<td>22.</td>
<td>23.</td>
</tr>
</tbody>
</table>

5. Serious Adverse Events and/or Secondary Outcome Events since 180 day follow-up: [Yes [ ] No [ ]]
   - New stroke, ischaemic or haemorrhagic [not the qualifying stroke leading to enrolment] [Yes [ ] No [ ]]
   - Acute coronary syndrome [MI confirmed on ECG and/or raised serum Troponin] [Yes [ ] No [ ]]
   - Upper gastrointestinal bleed requiring blood transfusion and/or endoscopy [Yes [ ] No [ ]]
   - Other major bleed (i.e. not upper GI or intracerebral)
     - Not requiring blood transfusion or procedural intervention [Yes [ ] No [ ]]
   - Fall [Yes [ ] No [ ]]
   - New fracture [confirmed on X Ray] [Yes [ ] No [ ]]
   - Epileptic seizure [focal or generalised] [Yes [ ] No [ ]]
   - Symptomatic hypoglycaemia [blood sugar < 3mmol/L] [Yes [ ] No [ ]]
   - Symptomatic hyperglycaemia [blood sugar >22mmol/L] [Yes [ ] No [ ]]
   - New hyponatraemia [Na < 125mmol/L] [Yes [ ] No [ ]]
   - Attempted suicide/self-harm [Yes [ ] No [ ]]
   - Other SAE [Yes [ ] No [ ]]

Please complete a “Serious Adverse Event and Secondary Outcome Event” Form immediately if a patient has answered ‘Yes’ to any of the above events that:
- are unexpected reactions to the AFFINITY trial medication (i.e. not consistent with the product information)
- result in death;
- are life threatening (i.e. the participant was at risk of death due to the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- require hospitalisation or prolongation of existing hospitalisation;
- result in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- results in a secondary outcome event for the AFFINITY Trial (new stroke, ischaemic or haemorrhagic [not the qualifying stroke leading to enrolment], acute coronary syndrome [MI confirmed on ECG and/or raised serum Troponin], upper gastrointestinal bleed requiring blood transfusion and/or endoscopy, other major bleed [i.e. not upper G or intracerebral] requiring blood transfusion or procedural intervention, new fracture [confirmed on X Ray], epileptic seizure [focal or generalised], new hyponatraemia [Na<125mmol/L] or attempted suicide/self-harm).

6. Pregnancy: Yes [ ] No [ ] N/A [ ]

Please complete a separate ‘pregnancy notification form’.

7. Health care Utilisation:

   a. Hospitalisation days since enrolment (not including hospitalisation for the initial/qualifying stroke) [ ]

   b. Days spent in care at home since enrolment? [ ]

   c. Formal carers – total number of visits per week? [ ]

Primary Outcome

8. Simplified Modified Rankin Scale questionnaire (Circle each response on pathway & final score)

   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 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 [ ]

Score [ ]

AFFINITY 365 Day Assessment Form Version 6, 18th November 2015
Secondary Outcomes

9. New clinical diagnosis of depression
   a. Has the patient been diagnosed with depression since the last assessment?       Yes ☐ No ☐
   b. Has the patient been treated for depression since the last assessment? (non-pharmacological) Yes ☐ No ☐
   c. Has the patient been prescribed an antidepressant drug for treatment of depression since the last assessment? Yes ☐ No ☐

   If yes, to Q8c please ensure you have documented this on the current medication list.

10. PHQ-9 (please circle) Over the past 2 weeks, have you been bothered by:

     Scoring - 0: not at all; 1: several days; 2: more than half the days; 3: nearly every day

<table>
<thead>
<tr>
<th></th>
<th>Little interest or pleasure in doing things?</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Feeling down, depressed, or hopeless?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Trouble falling or staying asleep, or sleeping too much?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Feeling tired or having little energy?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Poor appetite or overeating?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Feeling bad about yourself, or that you are a failure or have let yourself or your family down?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Trouble concentrating on things, such as reading the newspaper or watching television?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>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 a lot more than usual?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Thoughts that you would be better off dead, or of hurting yourself in some way?</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

   TOTAL ☐ If score ≥ 15/27 notify GP: Yes ☐ No ☐ NA ☐

   Not able to complete ☐

10. If you checked off 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 other people?

   Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult ☐
11. Cognition (TICSm)

Score '1' for each correct answer and '0' if incorrect in the boxes provided

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

Registration
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?  Cabin ☐  Pipe ☐  Elephant ☐  Chess ☐  Silk ☐
   Now tell me all the words you can remember.  Theatre ☐  Watch ☐  Whip ☐  Pillow ☐  Giant ☐

Attention/Calculation
5. Please take away 7 from 100  93 ☐
   Now continue to take 7 away from what you have left over until I ask you to stop.  86 ☐  79 ☐  72 ☐  65 ☐
6. Please count backwards from 20 to 1  no mistakes ☐

Comprehension, Semantic & Recent Memory
7. What do people usually use to cut paper?  Scissors ☐
8. What is the prickly green plant found in the desert  Cactus ☐
9. Who is the reigning monarch now?  E, QE, QE2 ☐
10. Who is the Prime Minster now?  Correct surname ☐
11. What is the opposite of east?  West ☐

Language/Repetition
12. Please say this 'Methodist Episcopal'  Exactly right ☐

Delayed Recall
13. Please repeat the list of 10 words I read earlier  Cabin ☐  Pipe ☐  Elephant ☐  Chess ☐  Silk ☐
   Theatre ☐  Watch ☐  Whip ☐  Pillow ☐  Giant ☐

Total Score ☐/39
12. Fatigue (Vitality Domain of SF 36) (please circle)

The following questions are about how you feel and about how things have been with you in the past four weeks. As I read statement, please give me the one answer that comes closest to the way you have been feeling.

| a. How much of the time during the past four weeks did you feel full of life? |
|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
| b. How much of the time during the past four weeks did you have a lot of energy? |
|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
| c. How much of the time during the past four weeks did you feel worn out? |
|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
| d. How much of the time during the past four weeks did you feel tired? |
|---|---|---|---|---|---|
| All of the time | Most of the time | A good bit of the time | Some of the time | A little of the time | None of the time |
13. Health-related quality of life (EQ-5D-5L): Under each heading, please tick the ONE box that best describes your health TODAY.

**Mobility**
1. I have no problems with walking around  □ 1
2. I have slight problems with walking around  □ 2
3. I have moderate problems with walking around  □ 3
4. I have severe problems with walking around  □ 4
5. I am unable to walk around  □ 5

**Personal Care**
6. I have no problems with washing or dressing myself  □ 1
7. I have slight problems with washing or dressing myself  □ 2
8. I have moderate problems with washing or dressing myself  □ 3
9. I have severe problems with washing or dressing myself  □ 4
10. I am unable to wash or dress myself  □ 5

**Usual Activities (e.g. work, study, housework, family or leisure activities)**
11. I have no problems doing my usual activities  □ 1
12. I have slight problems doing my usual activities  □ 2
13. I have moderate problems doing my usual activities  □ 3
14. I have severe problems doing my usual activities  □ 4
15. I am unable to do my usual activities  □ 5

**Pain / Discomfort**
16. I have no pain or discomfort  □ 1
17. I have slight pain or discomfort  □ 2
18. I have moderate pain or discomfort  □ 3
19. I have severe pain or discomfort  □ 4
20. I have extreme pain or discomfort  □ 5

**Anxiety / Depression**
21. I am not anxious or depressed  □ 1
22. I am slightly anxious or depressed  □ 2
23. I am moderately anxious or depressed  □ 3
24. I am severely anxious or depressed  □ 4
25. I am extremely anxious or depressed  □ 5

- 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 on the next page to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box.
26. YOUR HEALTH TODAY = □□□□

The best health you can imagine

The worst health you can imagine
### Overall health status (SIS) (please circle)

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</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>you rate the strength of your...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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>

Note: If you have no affected, or weaker, side then score your dominant side i.e. your right side if you are right handed, or your left side if you are left handed.

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.

<table>
<thead>
<tr>
<th>3. In the past week, how often did you...</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.

<table>
<thead>
<tr>
<th>4. In the past week, 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>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Say the name of someone 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>

Notes: If you do not do any or all of these code them as Extremely Difficult.

Item f. If you do not call but are handed the phone this is OK.

Item g. If you cannot hold a phone book, if you can read it this is OK. This item addresses whether you are able to initiate a phone call, look up the number, and dial this number correctly.
The following questions ask about activities you might do during a typical day.

5. In the past 2 weeks, how difficult was it to...

<table>
<thead>
<tr>
<th>Activity</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. 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. 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. Bathe yourself?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>d. Clip your toenails?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>e. 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. 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. 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. Do light household tasks/chores (e.g. dust, make a bed, take out the garbage, do the dishes)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>i. Go shopping?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>j. Do heavy household chores (vacuum, laundry or yard work)?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: If you do not do any or all of the activities listed, code them as Cannot do at all.

Item a. If you are on pureed food, even if you feel you could cut the food, code as Cannot do at all.

Item c. Bathing oneself does not include getting into the bath.

Item e. This question is associated with movement. Does the person have the physical ability to get to the bathroom quickly enough?

Item f. Losing a little urine/dribbling is considered an accident. If you have a catheter, code as Cannot do at all.

Item g. Constipation is not counted here, person has to have an accident.

Item i. “Shopping” means any type of shopping and does not include driving.

The following questions are about your mobility at home and in the community.

6. In the past 2 weeks, how difficult was it to...

<table>
<thead>
<tr>
<th>Activity</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. 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. 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. 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. 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. Walk one block?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>f. Walk fast?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>g. 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. 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. Get in and out of the car?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: If you have not done any of the items in the past two weeks code as Cannot do at all.
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 5 cent piece?</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Notes: If you have no affected, or weaker, side then score your dominant side i.e. your right side if you are right handed, or your left side if you are left handed.

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. In 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>

Notes: If you don’t do any of the specific items, and has never done, code as None of the time.
9. 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

Please inform the patient (and carer, if appropriate) that their participation in the AFFINITY trial is now completed and thank them for their contribution. Please enter this information onto the corresponding form via the AFFINITY website www.affinitytrial.org

End of 365 Day Assessment (thank you)