



Efficacy of Fluoxetine - a randomised Controlled Trial in Stroke

ESTABLISHING THE EFFECT(S) AND SAFETY OF FLUOXETINE INITIATED IN THE ACUTE PHASE OF STROKE

Study Protocol

Developed in collaboration with the FOCUS-UK trial

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PROTOCOL APPROVAL

Establishing the effect(s) and safety of Fluoxetine initiated in the acute phase of stroke

Efficacy of Fluoxetine – a randomisEd Controlled Trial in Stroke (EFFECTS)

EudraCT Number 2011-006130-16

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LIST OF MAIN ABBREVIATIONS

ACE	Angiotensin Converter Enzyme
ADR	Adverse drug reaction
ADL	Activities of Daily Living
AFFINITY	Assessment of Fluoxetine In sTroke recoverY trial (the AFFINITY trial)
CI	Chief Investigator
CRF	Case report form
CTIMP	Clinical Trial of Investigational Medicinal Products
DMC	Data monitoring committee
EQ5D-5L	EuroQoL Questionnaire for health related Quality of Life
ER/ARA	Emergency Room/Acute Receiving Area
FASS	Farmaceutiska Specialiteter i Sverige
fMRI	functional Magnetic Resonance Imaging
FOCUS	Fluoxetine Or Control Under Supervision (the FOCUS trial)
GCP	Good Clinical Practice
HRQOL	Health Related Quality of Life
IADL	Instrumental Activities of Daily Living
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IHD	ischaemic heart disease
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MAOI	Monoamine Oxidase Inhibitor
MoCA	Montreal Cognitive Assessment
MHI-5	Mental Health Inventory – 5 question version
MHRA	Medicine and Healthcare products Regulatory Agency
MPA	Medical Products Agency
MREC	Multicentre Research Ethics Committee
mRS	modified Rankin Scale
NHS	National Health Service
NIHSS	National Institute of Health Stroke Scale
NSAID	Non-Steroid Anti Inflammatory Drugs
OCSP	Oxfordshire Community Stroke Project
OD	once daily
PI	Principal Investigator/trial PI at local centre
PIB	Patient and next of kin trial Information leaflet/Booklet
QALYs	Quality Adjusted Life Years
RCT	Randomized controlled trial
MREC	Multicentre Research Ethics Committee
rt-PA	recombinant tissue Plasminogen Activator
R&D	Research and development department
SmPC	Summary of Product Characteristics
smRSq	simplified modified Rankin Scale questionnaire
SAE	Serious adverse event
SAR	Serious adverse reaction
SOP	Standard Operating Procedure
SSRI	Selective Serotonin Reuptake Inhibitor
SU	Stroke Unit
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBA	To be appointed
TBD	To be decided
TMF	Trial Master File
TMG	Trial management group
TSC	Trial Steering Committee
UAR	Unexpected Adverse reaction
WMD	Weighted Mean Difference

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SUMMARY

Title	Establishing the effect(s) and safety of Fluoxetine initiated in the acute phase of stroke
Short title	Efficacy of Fluoxetine – a randomised Controlled Trial in Stroke
Acronym	EFFECTS
Chief Investigator	Dr Erik Lundström, MD, PhD
Primary Research Question	Does the routine administration of Fluoxetine (20mg OD) for 6 months after an acute stroke improve patients' functional outcome?
Trial design	An investigator lead Sweden-based, multicentre, parallel group, double blind placebo controlled trial with broad entry criteria and follow up at 6 and 12 months.
Setting	Swedish stroke services
Eligibility criteria	<p>Inclusion</p> <ul style="list-style-type: none"> • age \geq 18 years • Informed consent can only be obtained from a patient who according to the trial investigator is mentally capable of decision-making and who, after having received information and got answers to their questions, wants to participate in the trial • brain imaging is compatible with intracerebral hemorrhage or ischaemic stroke • randomization can be performed in the stroke unit between 2 and 15 days after stroke onset • persisting focal neurological deficit is present at the time of randomization severe enough to warrant 6 months trial treatment from the combined physician's and patient's and carer's perspective <p>Exclusion</p> <ul style="list-style-type: none"> • subarachnoidal hemorrhage • unlikely to be available for follow up at 12 months • patient and/or carer unable to understand spoken or written Swedish • other life threatening illness • pregnant or breast-feeding or of child bearing age not taking contraception, minimum contraception is an oral contraceptive; an HCG-test is to be made prior randomization and after the end of trial medication • history of epileptic seizures • attempted suicide or self-harm • allergy or contra indication to Fluoxetine • taken a monoamine oxidase inhibitor in last 5 weeks or on serotonergic drug • current or recent depression requiring treatment with SSRI • already participating in a CTIMP
Randomization	Central, via a secure web based randomization system utilizing a minimization algorithm
Descriptions of interventions	Fluoxetine 20mg once daily or matching placebo capsules for 6 months. Drug dispensation in bottles for 3 months per dispensation, 2 nd after ruling out depression
Outcome measures	Primary outcome measure: modified Rankin Scale (mRS) Secondary outcome measures: Survival at 6 & 12 months; Stroke Impact Scale; EQ5D-5L; MHI 5; Vitality subscale of the Health Questionnaire, and cardio-vascular morbidity; DSM-diagnosis of depression; Adherence to medication; Adverse events; Resource use; and Investigations: NIHSS (motor function); one part of NGTA (comprehension, yes/no), MoCA (cognition), DSM-IV, and MADRS (if feasible) (mood), CGI frequency (emotionalism).
Baseline and Follow up	Local web based secure randomization (allowing balancing of trial arms for key prognostic variables by use of a minimization algorithm) at the hospital after written informed consent and face-to-face investigations; telephone contact at week 1 and 4, and months 3 and 7; at 6 month a face-to-face examination; Central at 6 and 12 months via postal mail or telephone for answers to questionnaires by patients and/or proxy, or with the help of the patient's medically responsible physician in case the patient is hospitalized and the forms cannot be filled in without help from the physician
Sample size estimate	90% power to detect an improvement in proportion of patients with an mRS of 0-2 at 6 months from 27% to 32.6%
No of participants	1500
Statistical methods	Based on an ordinal analysis of mRS, adjusted for baseline variables included in the minimization algorithm and stratified according to main deficit at entry
Timetable	Start up /Feasibility phase: 2014-2015 Main phase: 2015-2018

1. INTRODUCTION

1.1. Background

1.1.1. The burden of stroke, summary

About 30,000 people have a stroke each year in Sweden and, even with acute treatments there is a high mortality and a high percentage of survivors will have long-term residual disability. This places a huge burden on health and social services and informal carers. The estimated life-time direct costs for women with a first-time stroke were 49,000 euros (2009 prices), while for men they were even higher (60,000 euros, 2009 prices). Productivity losses due to stroke were estimated at 19,000 euros for women and 10,000 euros for men (2009 prices). [reference: Int J Technol Assess Health Care. 2014 Apr;30(2):203-9. doi: 10.1017/S0266462314000075. Costs for stroke in Sweden 2009 and developments since 1997. Ghatnekar O1, Persson U2, Asplund K1, Glader EL1.]

Although there is more that can be done to implement treatments that we know are effective e.g. the more widespread provision of thrombolysis and more rapid access to stroke units, there is still an urgent need to identify new treatments that might reduce neurological impairments, disability and dependency after stroke. One promising intervention that needs to be tested is a widely used antidepressant drug, fluoxetine, a serotonin reuptake inhibitor (SSRIs).

1.1.2. The necessity to establish new effective treatments in stroke

Stroke is a manifestation of cardiovascular disease with the brain as the target organ. Stroke is a devastating condition with acute phase mortality of 10 %. After one year at least 20 % are dead. Among the survivors serious sequels are present in up to around 40 % of patients according to new register data in Sweden, international frequencies are frequently higher. Stroke remains a worldwide problem. It has been estimated that each year stroke causes over four million deaths worldwide which globally makes stroke the second most common single cause of death after ischaemic heart disease (Murray 1996; Strong 2007). In Europe, a quarter of a million people will become disabled after their first stroke each year. In Sweden alone 30 000 persons get a stroke every year and around another 10 000 get a transitory ischaemic attack (TIA) which is a sinister warning signal of a stroke; around 10 % of the TIA patients get a stroke within two days if not getting an effective preventive treatment. In Sweden stroke constitute the third most common cause of death and the most common somatic cause for need of long-term hospital care. At present more than 20 % of stroke patients are below retirement age, a proportion predicted to increase due to delayed retirement age and a possible increase of stroke among the younger (Norrving 2013). Although the incidence of stroke is not increasing in the western world there is still an increase in the eastern countries (Asplund 1996). Also with the increase of age stroke is predicted to become much more common. Stroke affects the life of the individual patient, but also the life of their relatives and constitutes a great challenge to society (Norrving 2013). Stroke is likely to remain a common medical emergency for the foreseeable time despite better preventive treatment. New effective well tolerated stroke treatment is accordingly highly needed.

1.1.3. Evidence based treatments

For all strokes

Stroke unit (SU) care is the evidence-based foundation of treatment for all patients with a suspected stroke; for all strokes of all ages, and of all types and severity grades; stroke unit care yields 5-6 % increase in independent survival as compared to treatment in general medical wards (Indredavik 1999). The SU-effect is sustainable for 10 years or more (Indredavik 2003). According to the latest Riks-Stroke report 88 % of all strokepatients in Sweden are admitted to a SU; the present target is to increase the SU-rate to 90 %.

For ischaemic stroke

For ischemic stroke caused either by thrombotic or embolic material, constituting 85 % of all strokes there are so far only two evidence-based pharmacological treatments. One is aspirin which when initiated within the first 24-48 hours after stroke onset increases the absolute frequency of independent survival by 1.3 %, possibly mediated by its secondary preventive effect (Chen 2000). Despite its modest effect aspirin is an interesting option since it can be given to most ischaemic stroke if not on anticoagulants and is not least of interest in the developing countries due to its availability and low cost.

The so far only other pharmacological intervention in ischemia is thrombolysis (clot busting) licensed for use in highly selected patients less than or up to 80 years of age and within 3 hours, limits which in combination with other contraindications, yield a very small part of all patients with ischaemic stroke being eligible for treatment. Several countries in their national guidelines have kept to the same age-limit but extended the time-window up to 4.5 hours after the ECASS 3 trial (Hacke 2008) supported to a certain extent by the Cochrane systematic review for thrombolysis in ischaemic stroke (Wardlaw 2009). Now, after the publication in May of 2012 of the main results of the Third International Stroke Trial – thrombolysis (IST-3) (IST-3 Collaborative group 2012) and an updated Cochrane systematic review (Wardlaw 2012) the whole situation as to thrombolysis will be altered. The IST-3 material of 3035 patients randomized worldwide is unique as well to its size as to its patient composition; a quarter of the patients were randomized within the first 3 hours; 53 % were above 80 years of age; 43 % had a very severe stroke syndrome (TACI, Total Anterior Circulatory Ischemia) (Bamford 1987); accordingly there was a high rate of high score stroke: 32 % with an NIHSS (National Institute of Stroke Scale) score ≥ 16 ; 30 % were in atrial fibrillation (AF). In all 95 % of the IST-3 population were outside the EU license for thrombolysis in acute ischaemic stroke. Despite the possibly more vulnerable patient-group in IST-3 in relation to the patients in the 11 earlier recombinant tissue Plasminogen Activator (rt-PA) trials there was a remarkable consistency as to almost all outcomes between the results in the metaanalyses comparing the previous eleven rt-PA trials (in all 3977 patients) and IST-3. Only two outcomes in the whole metaanalysis displayed a statistical difference: death due to all causes except ICH where IST-3 was neutral, and the occurrence of cerebral oedema which was slightly more frequent in IST-3. The IST-3 computed tomography, CT, study in all patients with blinded re-evaluation the CT, in some centers MR (magnetic resonance imaging), and the longer follow up in IST-3, six vs. three months in previous trials may have given the basis for these further observations.

With ongoing IST-3 yearly presenting good reports from the Data and Safety Monitoring Committee (DMC) wider treatment limits have been successively applied also in open treatment series (VISTA). Hence, IST-3 and the Cochrane metaanalysis gives the long longed for evidence of wider criteria for thrombolysis. The findings are already successively underway to influence the stroke guidelines across the world. First, the upper age-limit of 80 years is about to be abolished, based on the finding that the above 80 years' population had benefits of at least the same degree as the patients of 80 years and below, especially if treated within three hours of onset. Since

strokepatients above 80 years constitute 40 % of stroke the number of eligible patients will increase, despite a concurrent increase of medical contraindication which must be considered in the elderly. The risk of early hazard in the form of intracranial hemorrhage (ICH) did not differ between patients above 80 years vs. the younger. There was no time-dependent increase in hazard out to six hours. Further in IST-3, although this remains to be discussed more in clinical detail, patients with severe stroke seemed to have a better or at least as good effect of treatment as the less severely struck. Among the more severely struck an important time dependant effect was clearly seen, even when adjustments had been made for more elderly patients and worse stroke having arrived earlier in hospital. Bearing in mind that the elderly, severely struck patients have the worse prognosis this finding may lead to elderly patients with severe strokes being considered for treatment in a new way than hitherto. IST-3 turned out neutral on its primary effect variable mRS 0-2, was statistically significant in its predefined secondary analyses of mRS 0-1 and in ordinal, shift, analysis which has been shown to give a more reliable outcome than the dichotomous outcomes of the mRS (SAP 2012). However, trial stringency has demanded subgroup analyses to be interpreted with great caution, and mainly those based on adjusted shift analyses are at all presented. In subgroup analyses a possibly higher frequency of ICH was identified in the severe stroke syndromes like TACI, still with an overall benefit effect up to six hours.

The results of IST-3 has lead to a revised section on thrombolysis in the UK National Guidelines (RCP 2012) stating that all stroke patients, irrespective of age and severity should be considered for thrombolysis within three hours. Further, the possibility to extend the time-window to 4.5 hours is to be considered mainly for the younger patients (RCP 2012). Thrombolysis, which also demands a brain imaging to rule out intracranial hemorrhage, is an expensive treatment and the 'quality of life-adjusted' cost-effectiveness is being investigated in a prospective sub-study in IST-3 (Murray, personal communication 2012). So far the treatment is not generally available across the world. Thrombolysis increases the absolute frequency of independent survival by 8 % in all patients and by 10 % among the elderly treated within 3 hours as compared to control. This high treatment effect is unusual in clinical medicine. Thanks to IST-3 the high number of uncertainties of the 2009 update of the Cochrane systematic thrombolysis review has now been reduced to primarily one: the early hazard control (Wardlaw 2009a; Wardlaw 2009b). Accordingly, two areas are the prime subjects of increased efforts: to reduce the early hazard, 7% of symptomatic intracranial hemorrhage (SICH) of which more than half, 4 %, are fatal; and to direct the health care efforts to shortening the onset-to-treatment-time. Further as to pharmacological clot-busting, different dosages and substances are investigated as well as local administration of the thrombolytic drug into the clot. Also, opening up the occluded vessel to extract the clot is being under development often with a combined stenting device. This approach is being tested in several trials.

For hemorrhagic stroke

The hemorrhagic stroke is usually manifested as an intracerebral hematoma with or without a breakthrough bleeding into the cerebral sinuses and/or into the subarachnoidal space. For intracerebral hemorrhage (ICH) which principally has the same risk factors as cerebral ischemia there are even fewer options of active treatment than for stroke due to ischemia apart from the essential SU care. The prognostic pattern of ICH is somewhat different to that of cerebral ischemia, a higher acute mortality and there are cases that recuperate better than after an ischaemic stroke but there is also very serious long-term outcome of ICHs. There is a lack of specific treatment in most cases of ICH, but trials are addressing this (STICH (1. Gregson 2012), 2. Mendelow 2013). Aiming to alleviate the space-occupying bleed some superficial hematoma can be surgically evacuated which for intracerebellar hematoma may be lifesaving (Socialstyrelsen 2006, 2009, 2011).

Sequels of stroke

Hence, we are looking at the results of an atherosclerotic disease with the brain as the target organ and where there is high mortality (after one year more than 20% of the patients will be dead) and among the survivors there is a high degree of impairment, e.g. hemiparesis, communication and cognitive deficits. For the ischemias there are some treatment available, for hemorrhage in practice almost nil. For the whole group there are also emotional residuals occurring in up to 60-80 %, at one year there is a risk of approximately 30-40 % having a long-standing depression and/or emotionalism. Up to 70 % have a lowered Quality of Life (Ahlsjö 1984).

New evidence on treatment is warranted as well for ischemias as hemorrhages:

It is obvious that there is a clear and urgent need for effective treatment in stroke patients to improve the prognosis. The drug under test in EFFECTS is a well-tested anti-depressant and a potential enhancer of plasticity. It is of utmost importance given that there will be physicians who are apt to jump to treating almost all patients with SSRIs to have these tested to confirm or refute the expectations arisen by the FLAME trial, specifically since there are side-effects. The risk-benefit ratio has to be established before any change in treatment criteria, so far in stroke depression and emotionalism, can be in effect. It must also be born in mind that the evidence for SSRIs in post stroke depression and emotionalism is not robust; the most comprehensive metaanalyses consist of a number of small trials, with a variety of outcome measures and there is a significant heterogeneity between trials (Hackett 2008a, Hackett 2010).

Publications plans in relation to the FOCUS and the AFFINITY trials

Working with the thrombolysis Third International Stroke Trial (IST-3) we have learned the complications of covering all regulations in different countries for an academic driven trial. We decided instead to be collaborators staying with one trial per country. Each trial will have its own statistical power. Since we share the main design and our minimal data set this gives us the means and total sample size of a very large multi-centre international trial (>6 000 patients) and it also allows us to compare the results of each trial, the external validity, between our countries. In order to give maximum reward to our potential grant giving bodies we will publish our joint findings as a collaborative group as we have done and do in the IST-3 trial (IST-3 Collaborative group 2012; Sandercock 2012, Wardlaw 2012, etcetera). The collaborative group will also publish within the Cochrane Collaboration. Thanks to our baseline and six months face-to-face investigations in Sweden the EFFECTS trial will give deepened light on the effect on the varying deficit and if any of them is most likely to respond to treatment. Further, only EFFECTS may include sub-studies to explore important mechanisms of action of fluoxetine, on simple tests of hemostasis and inflammatory parameters and on the brain and the lesion. The planned sub-studies will be described in protocols separate from this main trial protocol and will be subject to separate applications to the Ethics Committee and the Swedish Medical Products Agency (MPA).

1.1.4. Survey of the field

Selective serotonin reuptake inhibitors in depression and in stroke

Selective serotonin re-uptake inhibitors (SSRIs) were launched in the 1980-ies as new and more selectively acting antidepressant drugs. The good tolerability constitutes a substantial advantage which has permitted many more patients with depression to get a pharmacological treatment. The number of indications has increased during the years, specifically amongst the anxiety-syndromes, probably due to the many functions of the serotonin-system in the brain. A handful varying preparations with a common basic function – blocking of the transporters of serotonin – has been at test. However, the molecules are different in relation to pharmacokinetic and

pharmacodynamic properties. Fluoxetine is the substance that has come most into use, and the primary drug in clinical post stroke depression. Comparatively the substance, which has a very favorable adverse side-effects/adverse reaction profile, is characterized primarily by a long half-life regarding as well the mother-substance and its main-metabolite.

The fact that fluoxetine has been so much tested in post stroke depression is of a great advantage since the knowledge is wide as to its tolerability in patients with a brain-lesion and for both ischaemic and hemorrhagic stroke. Furthermore within the Cochrane Collaboration three systematic reviews regarding prevention and intervention respectively of post stroke depression, and treatment of emotionalism (Hackett 2008a, 2008b, 2010) presented the background, the effects and the adverse reactions with the SSRIs. This has not least been further investigated by Mead et al in the systematic review preceding this trial (Mead 2013). Fluoxetine has been the most investigated drug in these metaanalyses. In people with a psychiatric depression, the SSRIs have been shown to modulate the hyperactivity of the hypothalamic pituitary axis (Nikish 2005). In healthy humans functional magnetic resonance imaging (fMRI) studies have demonstrated how Fluoxetine modulates cerebral motor activity (Loubinoux 1999).

Selective serotonin reuptake inhibitors in animal models

In animals, selective serotonin reuptake inhibitors (SSRIs) have several potentially beneficial effects on both the normal and the diseased brain.

First, they have a neurotrophic effect. Neurotrophins are involved in embryogenesis and organogenesis. The SSRIs control neural plasticity in adults, regulate synaptic activity and neurotransmitter synthesis and are essential for the regeneration of nerves (Lang 2003). The effect of fluoxetine has been studied and it seems as if fluoxetine opens up a window-of-possible-effect irrespective of the age of the rats with amblyopia (Maya 2008; without fluoxetine there was but a short window of opportunity for visual training during the post-neonatal period; with fluoxetine effect was achieved also in the adult rat. The effects were accompanied by reduced intracortical inhibition and increased expression of brain-derived neurotrophic factor in the visual cortex. Adult neurogenesis is generally restricted to the subependymal cells of the ventricular system and the subgranular zone of the dentate gyrus in the hippocampus (Ming 2005). SSRI antidepressants increase neurogenesis and expression of neurotrophic/growth factors in the adult hippocampus (Schmidt 2007). This is likely to account for the behavioral benefits of antidepressants in animals (Santarelli 2005). In rats with induced fear fluoxetine allows fear to be erased by extinction-guided remodeling of the memory circuitry, but only if the pharmacological treatment was combined with psychological rehabilitation (Karpova 2011). Several studies have shown that migration of new neurons to damaged areas of the brain may occur (Wiltrout 2007), and that neurogenesis may also occur *within* areas of damaged brain in patients with ischaemic stroke (Taupin 2006).

Secondly, fluoxetine may have a neuroprotective effect associated with its anti-inflammatory effect (e.g. repression of microglia activation) (Lim 2009), enhancement of specific protein expression (hypoxia inducible factor – I alpha, hemeoxygenase-1) (Shin 2009).

Thirdly, SSRIs can indirectly affect the adrenergic system through up-regulation of beta1 receptors (Palvimaki 1994).

Selective serotonin reuptake inhibitors and effects on motor function in humans

In healthy humans, functional magnetic resonance imaging (fMRI) studies have demonstrated that fluoxetine can modulate cerebral motor activity (Loubinoux 1999). In 8 patients with pure motor stroke given fluoxetine, there was hyper-activation in the ipsi-lesional primary motor cortex during a motor task; moreover, fluoxetine significantly improved motor skills of the affected side (Pariente 2001). In a small scale randomized trial of patients with unilateral stroke, the administration of

citalopram, another SSRI, was associated with a significant improvement in neurological status as measured by the NIHSS and a decrease of motor excitability over the unaffected hemisphere measured by transcranial magnetic stimulation (Acler 2007). Zittel investigated the effects of a single dose of 40mg citalopram in 8 chronic stroke patients. Dexterity was significantly improved (Zittel 2009). In a trial of 52 hemiplegic patients, randomly allocated three treatments (20 mg/d fluoxetine vs 150 mg/d maprotiline vs. placebo) for 3 months on a background of physical therapy, those allocated fluoxetine demonstrated the greatest recovery in disability (Dam 1996). The fluoxetine on Motor Rehabilitation After Ischemic Stroke (FLAME) Trial is the largest trial to date to evaluate the effects of SSRIs on motor recovery after stroke (Chollet 2011). This double blind, placebo controlled, multicentre trial randomized 118 patients with ischaemic stroke and unilateral motor weakness to fluoxetine 20mg daily or placebo for 3 months. At day 90, the improvement in the Fugl Meyer motor score from baseline was significantly greater in the fluoxetine group (57 patients, adjusted mean of +34.0 [95% Confidence interval CI 29.7; 38.4]) than in the placebo group (56 patients, adjusted mean of +24.3 [95%CI 19.9; 28.7]; p=0.003). Also, the frequency of independent patients (modified Rankin scale: 0-2) was significantly higher in the fluoxetine group (26.3% vs 8.9%; p=0.015) although there were not significant differences at other cut-offs. Although promising, this study recruited, on average, just three to four patients per year from each of the participating centers, thus limiting the generalizability. All patients also received physiotherapy; so we do not know whether fluoxetine on its own has given the effect or whether it was the combination of fluoxetine and training resulting in the excellent results in FLAME. This is a highly interesting issue in all countries where training resources might be scarce. In Sweden the situation is rather scattered; all SUs have training facilities but length time of in-hospital stay is varying. There are out-patient training facilities and also an increasing amount of mobile rehabilitation teams but the issue of training in relation to fluoxetine –medication remains to be answered. Also, there is much debate on when after stroke onset and in what forms training should be undertaken.

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

Several recent small studies have suggested the fluoxetine might have other neurological benefits e.g. increased activation of agonist and antagonist muscles in paretic arms after stroke (Berends 2009), improvements in executive function after stroke (Narushima 2007), improvements in alexithymia (unawareness of emotional reactions which is common in right hemisphere strokes) (Spalletta 2006). We do not know whether these beneficial effects of antidepressants are independent of their antidepressant effect (Talleli 2009). In people with depression, SSRIs modulate the hyperactivity of the hypothalamic pituitary axis (HPA) (Nikisch 2005). After stroke, activation of the HPA axis occurs resulting in hypercortisolism. Hypercortisolism is associated with the development of delirium after stroke and also predicts worse long-term outcome. Thus, SSRIs might, by attenuating the hypercortisolism that is present after stroke, improve outcome, including cognition.

If fluoxetine would have the same mechanism in man as shown in the animal studies, specifically the robust findings on amblyopia (Maya 2008) and open up a window for training while also in other ways positively affect plasticity this must be found out and the finding be of guidance for clinical practice, is training of such importance as addition to fluoxetine that it is worth the cost to build out training facilities where they are scarce, or does fluoxetine in humans give benefits of the same caliber with ordinary training and activities. Also important we do not know whether any benefits of fluoxetine persist beyond the treatment period and whether fluoxetine might improve outcome in stroke patients *without motor* deficits but others. The promising, but inconclusive results clearly justify further larger trials in patients with motor deficits.

Systematic review of effects of fluoxetine on post stroke outcomes

In a systematic review of randomized trials testing whether a course of treatment with fluoxetine started shortly after stroke onset can improve function and prevent post stroke depression identified six randomized controlled trials (RCTs) published before December 2009 which together randomized 385 patients (Yi 2010). This metaanalysis demonstrated that fluoxetine helped recovery in neurological function. In a Cochrane Systematic Review of all Selective Serotonin Receptor Antagonists (SSRI) versus control in stroke (Mead 2012) 52 of the identified trials were possible to include in metaanalysis. Twenty-eight trials investigated fluoxetine including the FLAME trial. There were statistically significant benefits of SSRI on both of the primary outcomes: RR for reducing dependency at the end of treatment and for disability score with high heterogeneity between trials. For neurological deficit, depression and anxiety, there were statistically significant benefits of SSRIs. There was no statistically significant benefit of SSRI on cognition, death, motor deficits and leaving the trial early. There was a non-significant excess of seizures (RR 2.67; 95% CI 0.61 to 11.63) (seven trials involving 444 participants), a non-significant excess of gastrointestinal side effects (RR 1.90; 95% CI 0.94 to 3.85) (14 trials involving 902 participants) and a non-significant excess of bleeding (RR 1.63; 95% CI 0.20 to 13.05) (two trials involving 249 participants) in those allocated SSRIs. Data were not available on quality of life, fatigue or healthcare costs.

In the Mead et al systematic review there was no clear evidence from subgroup analyses that one SSRI was consistently superior to another or that time since stroke or depression at baseline had a major influence on effect sizes. Sensitivity analyses suggested that effect sizes were smaller when trials at high or unclear risk of bias were excluded. Only eight trials provided data on outcomes after treatment had been completed; the effect sizes were generally in favor of SSRIs but CIs were wide. The authors concluded that SSRIs appeared to improve dependence, disability, neurological impairment, anxiety and depression after stroke, but that there was heterogeneity between trials and methodological limitations in a substantial proportion of the trials. Large, well-designed trials are now needed to determine whether SSRIs should be given routinely to patients with stroke. The metaanalyses, comprising trials with different indications for the SSRI, mainly post stroke depression, demonstrated that at the end of treatment, patients allocated an SSRI were less likely to be dependent, disabled, neurologically impaired, depressed or anxious. However, there was substantial clinical and methodological heterogeneity, and treatment effects were smaller when only high quality trials were included. Furthermore, there appeared to be an excess of adverse events in those allocated an SSRI.

SSRIs and mechanisms of function including some aspects on hemostasis, in brief summary
SSRIs obviously have a range of possible mechanisms of action from on the brain-cell- level, in the synapses, the synthesis of transmitters, possibly on inflammatory processes and likewise of possible benefit in ischemia and up-regulating the adrenergic system. The metabolism of fluoxetine via CYP 2D6 warrants check of the patients' medications and possible dose-adjustments for drugs with the same metabolic pathway. Also the SSRIs assert an effect on the serotonin-levels in platelets via SERT, the target-protein for SSRI. Hence, with SSRIs lowered serotonin-levels in the platelets presumably increases the bleeding-time. Already fairly early in the SSRI era it was found that after about three weeks of SSRI-treatment the serotonin storages in the platelets were lowered with 89 % and after six weeks with 95 % (Wägner 1990). It is also known that there is an interaction with an unfavorable upper gastro-intestinal bleeding risk between SSRIs and NSAIDs which should be avoided. Further, although many post stroke depression patients are treated with fluoxetine while on aspirin or warfarin without any problems, there will yet be a specific observance in the trial for any adverse effects from these combinations. The hemostasis will be evaluated by simple routine blood sampling. In a recent review the epidemiologist Professor Andrade summarizes for cardiac disease that "SSRIs influence

cardiovascular functioning and health through several different mechanisms; for example, they inhibit serotonin-mediated and collagen-mediated platelet aggregation, reduce inflammatory mediator levels, and improve endothelial function. SSRIs improve indices of ventricular functioning in ischaemic heart disease (IHD) and heart failure without adversely affecting electrocardiographic parameters. SSRIs may also be involved in favorable or unfavorable drug interactions with medications that influence cardiovascular functions. The clinical evidence suggests that, in general, SSRIs are safe in patients with IHD and may, in fact, exert a cardio protective effect". These summary data in cardiology are generally very encouraging and contains the same caution we have. As we will have defined effects-criteria we will also register all adverse events, and any serious adverse events in order to for the trials to give a reliable risk-benefit balance for fluoxetine in stroke patients.

Two publications from 2014 can be mentioned. They have a different angle with pre-stroke SSRI (i.e. psychiatric patients getting a stroke while on SSRI-treatment, mainly for depression). One is a Danish register study where outcome was worse for patients who got a hemorrhagic stroke than for those where stroke was ischaemic (Mortensen 2014). Hemorrhagic stroke often has a worse outcome, the study is not conclusive but can be included as one more piece of information, the results are probably in line with a publication from South-Korea, a metaanalysis showing a general increase in stroke risk, as well ischaemic as hemorrhagic, with SSRI (Shin D 2014). The authors conclude that, due to heterogeneity among studies and that depression per se increases the risk of stroke, new well-designed studies are needed. Hence these publications do not alter the need for investigating as well ischaemic as hemorrhagic stroke in new stroke-treatment trials.

The need for further large trials with broad entry criteria

A debate in the journal Stroke whether or not further trials are needed for SSRIs for treatment of stroke is according to the above already answered, new large clinical trials are absolutely necessary (Chollet 2011, 2012, Marshall 2012, Selim and Molina 2012, Mead 2012). The 2012 Cochrane review clearly demonstrated methodological weaknesses in some of the previous studies, the confidence intervals around estimates of treatment effects were wide, there was heterogeneity between trials, and there was an excess of adverse events associated with fluoxetine. The risk-benefit ratio must be established. Importantly, we also need to know whether any beneficial effects of fluoxetine persist after treatment is discontinued. Important to notice: when serious clinicians and scientists, as those partaking in the mentioned debate, give the suggestion to go for new trials but maybe also to be a bit less strict with the post stroke depression diagnosis in order more stroke patients could be given an SSRI for stroke (as stated by Selim and Molina 2012) this single remark, whether a bit in jest, certainly reflects something. To the best of our knowledge this reflects clinical practice where the suggested policy is observed for ischaemic and hemorrhagic stroke alike.

Many small trials are by now part of several metaanalyses. Safety: no significant difference for hemorrhagic versus ischaemic stroke has been observed. The question of stroke-risk in psychiatric patients on SSRI has recently been lifted. Efficacy: the interaction for treatment of post stroke depression is stronger than for treatment of stroke, heterogeneity between trials with wide CIs occurs in both indications. Prevailing data are most probably overused and uncertain and can no longer give the basis of the balance of benefit and harm for SSRIs in stroke.

New data on the effect of SSRIs on outcome in ischaemic and hemorrhagic stroke are needed for evidence. Specifically the promising finding for fluoxetine to possibly reinforce brain plasticity in stroke must urgently be investigated as well for patients with ischaemic as hemorrhagic stroke.

Key unanswered questions about SSRI therapy for stroke
What is the 'time window' for fluoxetine?

*What is the effect of fluoxetine in patients with hemorrhagic stroke compared to ischaemic?
What is the effect of fluoxetine in different types and severity of stroke as classified according to the Oxfordshire Community Stroke Project (OCSP) and according to the type of occlusion?
What pre-treatment brain scan appearances predict response to treatment?
What is the effect of fluoxetine in patients with motor deficits, and aphasia respectively, and in other deficits?
What is the effect of fluoxetine on overall survival?
What are the side-effects of fluoxetine?
What is the risk-benefit ratio of fluoxetine-treatment?
What is the impact of fluoxetine on health economy as estimated by the use of the EuroQoL (EQ5D5L)?*

1.1.5. Why choose fluoxetine?

There are several SSRI antidepressant medications available. We have chosen to evaluate fluoxetine because it is one of the most widely studied. Its safety profile is very well established, and the drug is generally well tolerated, in long-term use, even in older subjects. There is better evidence for its effectiveness in stroke than for alternatives. As for fluoxetine its metabolism via CYP 2D6 will need the checking of whether the patient's other medications may be metabolized in the same way and carry a risk of interaction. A number of manufacturers produce the drug and the price is low which makes it particularly attractive to health services which are under severe cost pressures. Lastly, of all the SSRIs, it has the longest half life, so that gradual reduction in dose is usually not as required when withdrawing the study-drug (which may be inevitable in a trial) in such a high grade as with the other SSRIs to avoid the possibility of an SSRI withdrawal syndrome.

Fluoxetine and safety

(Please see also abbreviated version in FASS, web address: <http://www.fass.se> ; SmPC medinfo@discoverypharma.co.uk; Product résumé: Fontex®, Läkemedelsverket 2012-03-08).

There are potential risks associated with giving fluoxetine to a wide range of stroke patients. Its interaction with antiplatelet and anticoagulant medication might increase bleeding risk, although this is usually minor and limited to bruising. Gastro-intestinal bleeds have been reported with SSRIs when combined with NSAIDs. Like other antidepressants, fluoxetine may lower seizure threshold, and therefore could increase the frequency of post stroke seizures. Patients with a history of epileptic seizures are therefore excluded from the trial. An adverse effect on glycemic control in diabetics has been recorded. Hyponatremia is a recognized adverse effect and may prove to be more common among stroke patients who may be taken concomitant ACE-inhibitors, diuretics and proton pump inhibitors. Combinations of fluoxetine and serotonergic medication e.g. analgesics with tramadol (and sumatriptan, the migraine medication which is contraindicated in stroke), may possibly increase the risk of a serotonergic syndrome. This was a feared reaction in the earlier days of the SSRIs but so far has not been shown as a major problem. For patients regularly using tramadol (or sumatriptan) should preferably be transferred to other analgesics or else the trial responsible PI and the patient's GP will be advised for special caution. Subject to assessment by the responsible clinician, some stroke patients with severe renal or hepatic failure may not be able to participate in the trial. Reassuringly, fluoxetine has been very commonly prescribed for several years to patients with stroke to treat depression and emotionalism without major problems emerging (Coupland 2011). **Recommended safety information** is given in the Product résumé: Fontex® where as well frequencies and further description are given of the different types of side-effects that can be expected (see Reference list: 'Reference Safety Information', SmPC Products Résumé Fontex®: Detailed Guidance from the European Commission CT-1 (2010) and CT-3 (2011)).

Driving after stroke is subject to individual assessment but a minimum of one month after a TIA is recommended in Sweden. For manifest stroke the recommendation is not to resume driving until further assessment has been made at the follow up visit, often after some six weeks. All decisions are thereafter based on the individual situation. This policy is good also for the trial; any effects of the study drug on the patients' psychomotor function can be simultaneously considered.

1.2. HYPOTHESIS

Routine administration of fluoxetine 20mg once daily in the 6 months after an acute stroke improves the patient's functional outcome.

1.2.1. RATIONALE

The need for large randomized trials of fluoxetine in stroke

Given the encouraging data, which suggest that fluoxetine might have substantial benefits for a wide range of stroke patients there is an urgent need to carry out randomized trials which have adequate power to reliably detect clinically important benefits also given that fluoxetine is inexpensive (around SEK 30 per month in Sweden), simple to administer and generally well tolerated, if it had an effect which was a fraction of that seen in the FLAME trial it would still be a very worthwhile treatment with benefits for the patients, their carers, the national health care, social services, and public finances.

The need to identify the patients who might particularly benefit, or be harmed, from treatment

Whilst fluoxetine may improve outcome for the whole range of stroke patients, it is also plausible given its diverse pharmacological effects that the balance of risk and benefit may vary in patients with different types of stroke. For instance, pre-clinical and clinical work has to a large extent been carried out for motor recovery, so to test the enhancement of other functional deficits is pivotal, but there is nothing to suggest that fluoxetine per se would yield a higher risk in other deficits; hence fluoxetine should definitely be investigated in large patient materials and broad entry criteria. Fluoxetine influences bleeding risk, particularly in those taking antithrombotic medication, so there could be differences in effectiveness between patients with ischaemic (who are taking antithrombotics) and those with hemorrhagic stroke. Patients with severe stroke associated with cognitive and communication problems may be at greater risk of adverse effects because the patients are unable to report early problems but they might also have more to gain from a treatment which hypothetically enhances recovery. Patients with severe stroke are normally at greater risk of post stroke depression (which among other things is associated with the grade of the disability) but – as a consequence of their deficits – are at greater risk that their post stroke depression is not recognized and so goes untreated. The preventive effect of post stroke depression may come to use not least for the severely struck patients. The preventive effect was observed in a systematic review and metaanalyses (Hackett 2008a, 2008b, 2010) and there was a lower frequency of depression in the actively treated group in the FLAME trial (Chollet 2011). Also, stroke patients with severe stroke syndromes and > 80 years are those with the worst outcome and as a group the natural course of disease gives a worse risk-benefit ratio than for most groups of stroke patients. However, it is of interest that interview-studies regarding thrombolysis have revealed a willingness to accept an increased risk of death in the acute phase for the possible long-term benefit of improved function (Koops 2002). In a fluoxetine-trial there is no such expected hazard. However, hazards in terms of adverse events and reactions, and serious adverse events and reactions will be monitored and suspected unexpected serious

adverse reactions (SUSARS) will be reported. A long clinical experience with high tolerability in emotional reactions gives the basis of a hypothesized benign profile, but since the effect size is yet to be defined for the stroke treatment indication the risk-benefit ratio remains uncertain. Our capacity in EFFECTS to define this ratio is strengthened by the two trials in the same family, the FOCUS and the AFFINITY trials which in all should give us up to 6 100 observed patients.

2. STUDY OBJECTIVES

The trial aims to robustly address several research questions.

2.1. Objectives

2.1.1. Primary:

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

2.1.2. Secondary:

Can routine treatment with fluoxetine 20mg once daily during six months initiated during the acute phase of stroke improve the patients' clinical outcome as to:

1. If fluoxetine improves functional outcome, does any improvement persist after treatment is stopped?
2. Does the routine administration off fluoxetine (20mg OD) for 6 months after an acute stroke causing motor impairment improve patients' motor function and does any improvement persist after treatment is stopped?
3. Does the routine administration of fluoxetine (20mg OD on simple tests of haemostasis and inflammatory parameter) for 6 months after an acute stroke causing communication impairment improve patients' communication function and does any improvement persist after treatment is stopped?
4. Does the routine administration of fluoxetine (20mg OD) for 6 months after an acute stroke causing impairments which precludes the formal assessment of post stroke mood improve patients' functional outcomes?
5. Does the routine administration of fluoxetine (20mg OD) for 6 months after an acute stroke improve patients' outcome with respect to mood, fatigue, cognition, health related quality of life or participation in an active life and does any improvement persist after treatment is stopped?
6. Does the routine administration of fluoxetine (20mg OD) for 6 months after an acute stroke reduce the cost of health and social care over the first year?
7. Does the routine administration of fluoxetine (20mg OD) for 6 months after an acute stroke increase the risk of serious adverse events?

2.2. Measure of outcome

2.2.1. Primary measure of outcome (in concordance with FOCUS and AFFINITY)

Modified Rankin Scale (mRS) (van Swieten 1988) (based ordinal analysis to maximize power and to avoid problems including patients with an mRS > 2 prior to their stroke) at 6 months after randomization. Patient who die would be attributed a score of 6 for this analysis.

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

Any misclassification of patients into an inappropriate mRS category may reduce the power of the trial. To minimize misclassification and intermodality differences we will use the simple modified Rankin Scale questionnaire (smRSq) described by Bruno and colleagues. This has been delivered by both telephone and postal questionnaires and has been completed by patients and proxies (Bruno 2010, 2011; Dennis 2012). The smRSq has been validated in English (Bruno 2010, 2011; Dennis 2012) but not in Swedish. We are planning to test the agreement of the Swedish small modified Rankin Scale questionnaire with face-to-face modified Rankin Scale RSq. (Lundström manuscript synopsis 2017).

Synopsis of manuscript with preliminary title:

Agreement of the Swedish small modified Rankin Scale questionnaire with face-to-face modified Rankin Scale

The smRSq is sent to patient by the Trial Manager Assistant (TMA) at 6- and 12 month post randomisation. If the patient do not answer, the TMA contact the patient by phone and remind them to send in the questionnaire. If they have difficulty to answer for themselves TMA helps them fill in the form by phone.

Statistics

Number of patients

The primary aim of the study is to evaluate whether the mRS-score measured by the smRSq differs from a mRS-score measured by a clinician. It has been defined that one step or more disparity in the mRS-score is a significant difference. A study of similar character has never been performed before and due to the nature of the study, an initial study, the sample size is not formulated in the guise of power, risk level, or clinical difference. The number of patients participating in the study is therefore primarily chosen for clinical reasons, not statistical, and 60 patients will be included in the study. In order to compensate for included patients not valid for efficacy analysis it is planned to enrol up to 65 patients in the study in order to have 60 patients valid for efficacy analysis. The attrition rate is estimated to be about 6%.

Statistical methods and data management

Statistical comparisons in order to test differences between dependent observations will be made by use of pair-wise Student's t-test for correlated means and statistical comparisons between two independent groups will be made by use of the Student's t-test for uncorrelated means., after validation for normal distribution by use of the Shapiro Wilk test. The Pearson correlation coefficient will be used in order to test independence between variables. In addition to that descriptive statistics will be used to characterize the data. All analyses will be carried out by use of the SAS system (The SAS system for Windows 9.4., SAS Institute Inc, Cary, NC, USA.) and the 5% levels of significance will be considered. In the case of a statistically significant result the probability value (p-value) will be given. The results will be presented in a cross table. The proportion of full agreement will be given in percent and 95% Confidence Interval, as well as weighted and not weighted Kappa value.

2.2.2. Secondary outcome measures (in concordance with FOCUS and AFFINITY)

By questionnaires (at 6 and 12 months, local send out and central follow up)

- Deaths from all causes by 6 and 12 months. Death from all causes until the end of the trial ascertained via the medical record system at the local centers which is linked to National Registry (Folkbokföringsregistret) (local follow up),
- The EuroQoL (EQ5D-5L) to provide an overall measure of health related quality of life (HRQOL) and to allow a health economic analysis based on quality adjusted life years (Herdman 2011)
- The mental health inventory 5 (MHI 5) will provide a measure of depression and anxiety. This brief measure performs well, compared with longer questionnaires (e.g. MHI-18, GHQ-12, GHQ-30, in the detection of depression and anxiety (Berwick 1991, McCabe 1996, Hoeymans 2004)
- The vitality subscale of the Health Questionnaire, equivalent to SF 36, will be used to assess patients level of fatigue (Mead 2007; 2011, Sahlgrenska Academy, personal message, 2012)
- The Stroke Impact Scale (SIS) will provide an overall assessment of patient outcome as well as allowing us to assess the effect of treatment on specific outcomes of importance to the patients. The SIS is a stroke-specific, comprehensive, health status measure. The scale was developed with input from both patients and caregivers and includes 8 domains (strength, hand function, ADL/IADL, mobility, communication, emotion, memory and thinking, participation) from across the full impairment-participation continuum (Duncan 1999; 2003). It also provided an overall assessment of recovery. The scale has been evaluated successfully for use by proxy respondents and has been delivered as both telephone and postal questionnaires (Duncan 2002; 2005, Kwon 2006).
- New diagnosis of depression since randomization. We will record whether a depression has been treated by the PI; or resulted in a referral for specialist assessment and whether the diagnosis was confirmed by a psychiatrist and whether antidepressant medication was initiated; whether there was any attempt at suicide or self-harm. We will also, prior to dispensation of the study-medication for the second three-months' period undertake an investigator-lead 10-item MADRS, and a DSM-IV diagnosis to identify or rule out a depression. Records will be made as to action/s taken in relation to the study-medication. (Montgomery 1979; American Association of Psychiatry, DSM-IV 1994, DSM-IV TR 2000) (as reported by the local center).
- Other adverse events to be recorded include: further strokes, acute coronary events, upper gastrointestinal hemorrhage, falls resulting in injury, new fractures, epileptic seizures, symptomatic hypoglycemia (<3 mmol/l), hyperglycemia (>22mmol/l) hyponatremia (<125mmol/l) (as reported by the local center).
- Direct healthcare and non-healthcare resources used during follow up including: transportation to hospital (ambulance or own), inpatient care (days in intensive care unit and in general hospital ward), outpatient care (visits to neurologist, other medical specialist, general practitioner, speech therapist, other), rehabilitation (visits to physiotherapist, other rehabilitation specialist), consumption of other prescribed and over the counter medication, nurse home visits, home care visits, hours informal caregivers spend for the care of the patient, home alterations to improve mobility/other. Long-term

data will also be retrieved from the Cause of Death Register and the National Patient Register, up till 3 years after inclusion of the last patient.

- Indirect resources during follow up including: hours lost from work for the stroke patient (if still working), leisure time lost for the patient (working and non-working stroke patients), and disability pension.
- Adherence to EFFECTS trial medication.

2.2.3. By investigation face-to-face (at baseline and at 6 months at local centre)

Composition of tests TBD after the feasibility phase, not to burden the patient

- National Institute of Health Strokes Scale (NIHSS) to assess motor function and for randomization also aphasia (www.ninds.nih.gov).
- Norsk Grunntest for Afasi, one part to assess the patient's yes and no-communication-capability and comprehension, (Reinvang 1985).
- MADRS + DSM-IV/DSM-V to identify depression, minor and major, (Montgomery 1997, American Psychiatric Association 1994).
- Montreal Cognitive Assessment (MoCA) to assess the patients' cognitive function (Aggarwal 2010).

3. STUDY DESIGN

Description of the proposed trial

Proposed trial design: EFFECTS (**E**fficacy o**F** **F**luoxetine – a randomized **C**ontrolled **T**rial in **S**troke) a prospective randomized multicentre double-blind parallel-group trial with broad entry criteria and follow up to ascertain the primary and secondary outcomes at 6 and 12 months.

Trial phases:

3.1. Start up- or feasibility phase

A startup phase will establish whether our protocol is feasible. It will enable us to establish: a core trial management team, an IT system to manage the web- based randomization, 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 including the extent of the face-to-face follow ups at 6 months.

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

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

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

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

Provided that the start-up phase proceeds as expected and

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

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

3.2. Main phase:

The main phase will be powered to detect differences in the primary outcome of modified Rankin scale for the entire group and also powered to detect differences in specific outcomes in three specified strata based on the patients' main neurological deficit at baseline. Because it may not be feasible to enrol sufficient patients to reliably detect moderate effects sizes in these strata on our primary outcome (modified Rankin Scale) we will introduce two strategies:

1. Collect outcome measures which are likely to be more sensitive than our primary outcome to the possible benefits of fluoxetine in specific strata.
2. To work collaboratively with the parallel trials FOCUS-UK and the Australian AFFINITY (we all have two representatives in our respective TSC) and the three trials share a minimal data set and basic design. This will increase the overall sample size and the number of patients in each of the important strata and aims at shortening time from trial onset to results. We will perform an individual patient metaanalysis and other pre-specified metaanalyses to maximize our chances to detect benefits in specific strata and thereby specific subgroups.

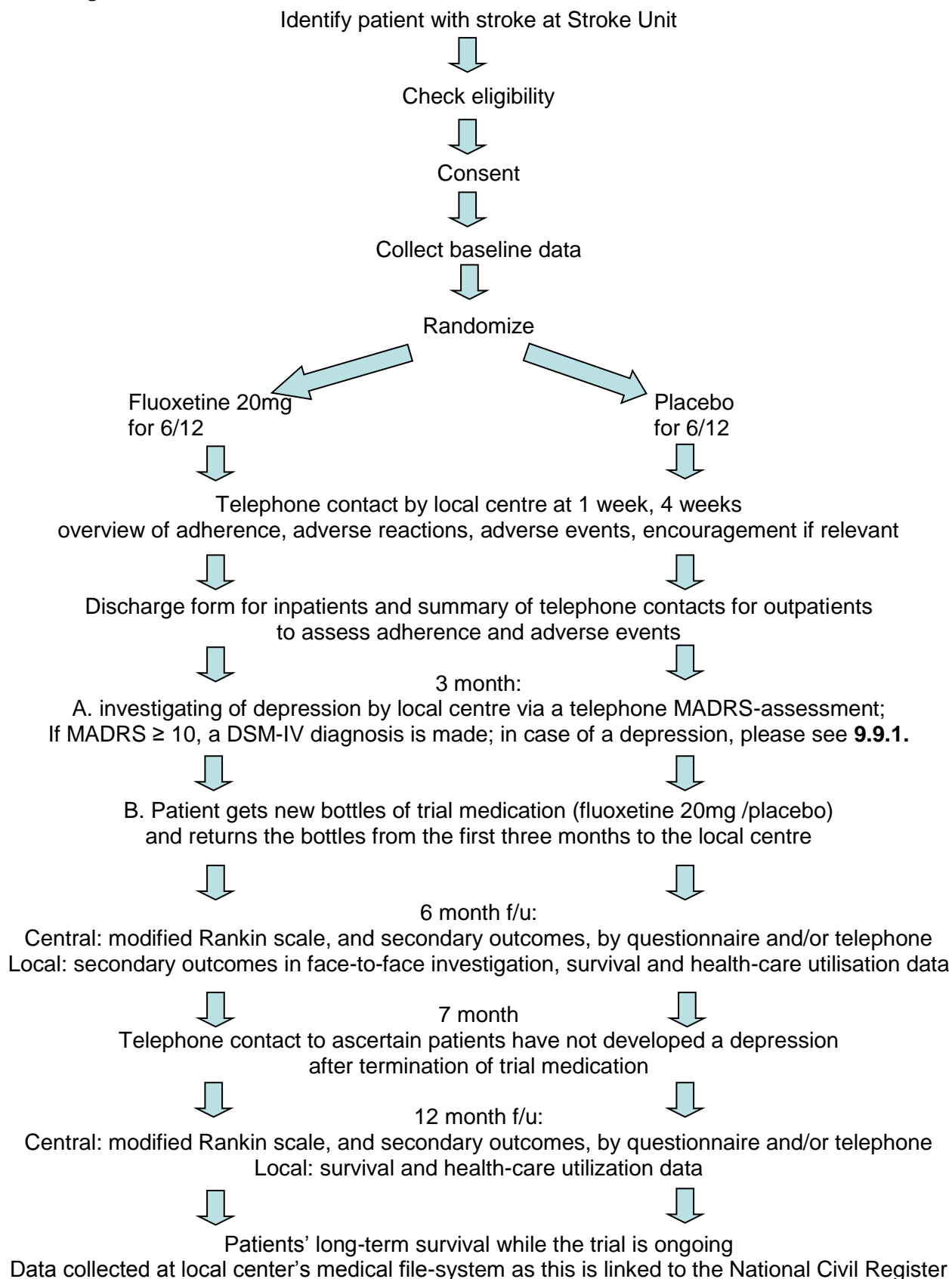
Filing system at each centre

There will be one Trial or Investigator's Site File and the Patient's Trial Files. The Site File should contain all trial documents such as the signed Study Protocol, the Trial Summary in Swedish and English; copies of approvals from the Multicentre Regional Ethics Committee, the Medical Products Agency, and a copy of any approved amendments.

A list of all patients included at each centre should be consecutively filled in and kept in the Investigator Site File. There will be a screening-list at each center to see the center-activity and in case of low recruitment to identify whether there are any systematic causes to the low entry rate which may be possible to address. However, since the trial does not seek to investigate the frequency of occurrence of symptoms permitting participation a complete log-list is seen as a risk of being time-consuming and time better given to information to patients filling the criteria.

The main centre will hold the Trial Master File (TMF) with all documents in original.

Flow diagram



4. STUDY POPULATION

4.1. Number of participants

The start up/feasibility phase will enroll about 50 patients. The main phase will enroll an additional about 1450 patients. A total of 1500 patients will be enrolled.

Eligibility criteria

4.2. Inclusion criteria:

- Age \geq 18
- Informed consent can only be obtained from a patient who according to the trial investigator is mentally capable of decision-making and who, after having received information and got answers to their questions, wants to participate in the trial
- Brain imaging is compatible with intra cerebral hemorrhage or ischaemic stroke
- Randomization can be performed between 2 and 15 days after stroke onset and by the research group at the patient's local/emergency hospital.
- Persisting focal neurological deficit is present at the time of randomization severe enough to warrant treatment from the physicians and the patient's and relative's perspective.

4.3. Exclusion criteria:

- Subarachnoidal hemorrhage (except where secondary to a primary intracerebral hemorrhage).
- Unlikely to be available for follow up for the next 12 months e.g. no fixed home address.
- Unable to speak Swedish and no close family member available to help with follow up forms.
- Other life threatening illness (e.g. advanced cancer) that will make 12-month survival unlikely.
- History of epileptic seizures.
- History of allergy or contraindications to fluoxetine including:
 - Hepatic impairment (S-ASAT/ALAT > 3 upper normal limit)
 - Renal impairment (S-Creatinine levels > 180 micromol/L)
- Pregnant or breastfeeding, women of childbearing age not taking contraception. Minimum contraception is an oral contraceptive. An HCG-test is to be made prior randomization and after the end of trial medication
- Previous drug overdose or attempted suicide.
- Already enrolled into a CTIMP.
- Current or recent (within the last month) depression requiring treatment with an SSRI antidepressant.
- Current use of medications which have serious interactions with fluoxetine
 - Use of any mono-amino-oxidase inhibitor (MAOI) during the last 5 weeksCo-administration of Fluoxetine and a mono-amino-oxidase inhibitor (MAOI) may result in life threatening interactions. Therefore, patients on MAOI inhibitors are ineligible for the EFFECTS trial. Also, any patient in need of treatment with a MAOI must stop their trial treatment for at least 5 weeks before commencing the MAOI, or to be treated as in-patients by a psychiatrist.
 - Fluoxetine is contra-indicated in combination with metoprolol used in cardiac failure New York Heart Association Grade IIIB and IV. At higher doses of metoprolol used in heart failure indication one should be vigilant of the interaction and early after enrollment monitor the patient with clinical monitoring including ECG.

Caution with the concomitant use of serotonergic analgesics containing e.g. tramadol, and anti-migraine medication with e.g. sumatriptan.

There should also be an awareness of a possibly existing interaction between SSRIs and NSAIDs manifested as an upper gastrointestinal bleeding in very rare cases (Abajo 1999).

4.4. Co-enrolment

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

However, if a participant has already been enrolled into another CTIMP, they cannot be enrolled into EFFECTS. If a patient is enrolled into EFFECTS, they may not subsequently be enrolled into another CTIMP. Also, local researchers must avoid overburdening patients. It is allowed to co-enroll patients in EFFECTS and the TIMING-study. The intervention in TIMING is early vs delayed start of NOAC in patients with acute stroke and Atrial fibrillation. Thus, all patients would receive NOAC either ≤ 4 days or > 5 days from the acute stroke.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1. Identifying participants

The responsible trial nurse/s and PIs identifies potentially eligible patients while the patient is still in the acute hospital, or possibly in a nearby rehab/geriatric clinic. After assessing the eligibility criteria including a ruling out a post stroke depression (the vigilance of mood disorders is regarded as standard care at most SUs in Sweden) the PI and the research nurse decide whether or not it is possible to proceed with the information of the trial.

5.2. Consenting participants

The Investigator or delegated sub-Investigator (in either case a physician) is responsible for ensuring informed consent is obtained and the consent form completed, signed and dated by all parties. The decision to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

EFFECTS will be run according to the standards laid out in the Guidelines for Good Clinical Practice in Clinical Trials and in keeping with the principles of the EU directive on Clinical Trials. The approval of the Ethics Committee is required for the whole trial and for each participating centre before recruitment can begin at that centre. Consent is supported by oral information and by the written patient's and relation's information leaflet/booklet, the "Patient and next of kin trial Information", the PIB.

The oral explanation to the participant should be performed by the Investigator. The participant must be given the opportunity to clarify any points they do not understand and have the chance to ask for more information from the physician. It should be emphasized that the participant may withdraw their consent to participate at any time without explanation and that this will not lead to any loss of benefits or loss of any measures to which they otherwise would be entitled.

The participant should be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s) but understand that their name will not be disclosed to anyone who is not involved in the trial. The patient should be given sufficient time to consider giving their consent for the study.

The patient must be able to make their decision whether to participate and to sign and date the consent form. The Investigator or delegated physician of the trial team should also sign and date the informed consent form (ICF) to confirm that informed consent has been obtained. The participant will receive a copy of the ICF, and the original is to be filed in the Investigator Site File (ISF). Full details of the consent process should also be recorded in the patient's medical records, please see **6**, Randomization.

5.2.2. Signed consent forms

The patient and if relevant their closest relation receive a copy of the completed ICF which includes the PIB.

5.2.3. New Safety Information

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

6. RANDOMIZATION

Randomization

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

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

Detailed notes of the consent procedure and the patient's participation in the trial must be recorded in the patient's medical record for medical information purposes and for any future source data verification. This note by the responsible trial physician, or a physician on delegation, should include information on: who gave the verbal and written information; who obtained the consent, and the date of consent; and who made the confirmation that the patient was eligible for enrolment. In the case the patient was incapable of signing him/herself this should be noted as well as the relationship between the patient and the person who signed in his/her place.

Following randomization in the proportion 1:1, the IT-system will generate an email to the main center that a patient has been randomized (center name and number and the patient's trial id), a letter for the local center to send the patient's GP of the patient's enrolment in the trial, along with a Trial Summary.

Treatment Allocation

The minimization algorithm randomly allocates the first patient to a treatment, but allocates each subsequent patient to the treatment that leads to the least difference between the treatment

groups with respect to the prognostic factors (Altman 2005). To ensure that we retain a random element to treatment allocation, patients will be allocated to the group which minimizes differences between groups with a probability of 0.8. The system contains a list of treatment codes for each center and which match the stocks held at that center. At the end of the session each patient is allocated a treatment code which corresponds to either an active (fluoxetine 20mg once daily) or placebo treatment pack which contains two times a three months' supply plus for the first 3 months a 14 days extra supply as back-up of the six' months' supply of capsules held at that center. The dispensation of the trial drug twice during the six months treatment time is consistent with the Swedish prescription system of three months' supply; and gives the opportunity of an increased awareness as to depression since an assessment will have to rule out a depression prior to sending the patient the trial medication bottles for the last three months. An extra supply of 14 capsules for the first three months will ensure that there will be no gap in trial medication if anything would delay the depression assessment and/or the supplying of the trial medication for the last three months. Further the two-times-dispensation is thought to increase the return of trial medication bottles of the first three months in a free-post envelope as soon as the new bottles have arrived.

Each centre will be sent six months' supply for ten patients from Apoteket AB at Karolinska University Hospital Solna which is the Swedish assembly address for the deliveries from Sharp International (former Bilcare) in the UK, please see further **9.3 and 9.4**. The randomization system will take account of the drug stocks held locally to firstly ensure the allocated treatment is available and second to minimize wastage. The randomization system will also automatically generate an email/fax to the centre coordinator, usually the responsible trial nurse at that center, to ensure the allocated treatment is used, and prescribed by the trial PI or a delegated trial physician.

To facilitate drug reconciliation and stock control the research nurse will remove the adhesive treatment number label from the medication bottle, stick it onto the above mentioned confirmation of allocation fax and fax it back to the IT-central. The trial IT-management system will prompt them to do so via email and/or fax until the return-fax is received.

Blinding

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

In case of lost medication

The responsible trial nurse, or Apoteket AB at Karolinska University Hospital Solna, may access treatment codes in order to replace lost study medication through the trial secure website by entering the patient's study ID number and date of birth. This does not mean any un-blinding, but only that the randomization system can generate a new treatment number where the contents is the same as in the treatment number primarily assigned. The medication is thereafter sent to the trial pharmacy at Karolinska University Hospital Solna, from them to the local hospital and further to the patient in a quick succession.

7. PREMATURE WITHDRAWAL OF PARTICIPANTS

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

8. STOPPING TRIAL TREATMENT EARLY

Patients or their closest relation may decide that the patient will stop taking the allocated treatment or the patient may be advised to stop taking the treatment by their doctor. If this happens, the patient will continue to be followed up as per protocol and their data included in the primary analyses. The reason for stopping the treatment prematurely will be recorded in the patient's electronic Case Report Form (eCRF). If treatment is stopped as a result of a SAE or SUSAR, the event will be reported as per protocol. Such cases are not regarded as premature withdrawals. We recommend coming off IMP for 14 days to see if the symptoms resolve. If they do then ideally they would restart to see if symptoms return. However, we recognize very few patients are prepared to do so. All stops (temporary and permanent) of the IMP must be registered in the e-CRF. There is not any limit for how long a temporary stop might be.

9. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

9.1. STUDY DRUG

Fluoxetine International Non-proprietary Name (INN): Fluoxetine

9.1.1. Study Drug Identification

MARKETING AUTHORIZATION NUMBER(S)

EFFECTS:

(FOCUS: PL 06831/0067)

Study Drug Manufacturer

The fluoxetine and placebo will as in the FOCUS trial be purchased from

Discovery Pharmaceuticals Ltd

The Old Vicarage, Market Place, Castle Donington, Derbyshire, DE74 2JB

Telephone: +44 (0) 845 2416616

Fax: +44 (0) 845 2419919

Medical Information Direct Line: 0

Medical Information e-mail: medinfo@discoverypharma.co.uk

Medical Information Fax: +44 (0)1256 775 569

Marketing Authorization Holder

Genus Pharmaceuticals Limited, T/A Genus Pharmaceuticals, Park View House, 65 London Road, Newbury, Berkshire, RG14 1JN UK

Summary of Product Characteristics

The summary of product characteristics is given in the Appendix 1. To access the latest electronic version please go to:

<http://www.medicines.org.uk/emc/medicine/13431/SPC/Oxactin+Capsules+20mg/>

to the web-site for Fontex®, where specifically the below mentioned references are of importance:

For Reference Safety Guidance Information on Fontex®, see Ref list: ‘Reference Safety Information’, SmPC Products Résumé Fontex®: Detailed Guidance from the European Commission CT-1 (2010) and CT-3 (2011), and “Prövarpärmen”.

9.2. PLACEBO

This will comprise a matching capsule containing the same excipients as the active drug (i.e. lactose, cellulose, magnesium stearate, colloidal silica), please see <http://www.medicines.org.uk/emc/medicine/13431/SPC/Oxactin+Capsules+20mg/> section 6.1.

9.3. Labeling and Packaging

This will be managed by a commercial trials organization in the UK that will:

- Purchase commercial fluoxetine 20mg capsules (Oxactin) or matching placebo capsules manufactured by Unichem in Goa and supplied via Niche Generics and Discovery Pharmaceuticals in the UK. Commercial capsules will be taken as QA reference sample.
- These procedures will be performed by Sharp International (contact person Peter Horton) where the trial medication after QP assessment will also be bottled according to the following:
- The total amount for six months and 14 days extra is 200 capsules of fluoxetine 20mg and 200 capsules of matching placebo:
 - Insert 100 fluoxetine 20mg capsules (covers the first 3 months and 14 days back-up supply) into labeled bottles with child-resistant tamper-evident lids with induction seals and containing desiccant
 - Insert 100 placebo capsules (covers the first 3 months and 14 days back-up supply) into matching labeled bottles with desiccant
 - Insert 100 fluoxetine 20mg capsules (for the last 3 months) into labeled bottles with child-resistant tamper-evident lids with induction seals and containing desiccant
 - Insert 100 placebo capsules (for the last 3 months) into labeled bottles with child-resistant tamper-evident lids with induction seals and containing desiccant
- Also the labeling of the bottles according to the randomization list, acquired from the IT-centre in Edinburgh, will rest on Sharp International.
- Sharp International will send the requested number of packages to an equivalent of Apoteket AB at Karolinska University Hospital Solna where there will be further check as to packaging.

9.4. Storage

The commercial trials organization, Apoteket AB at Karolinska University Hospital Solna, will:

- Store at 15 to 25°C awaiting a client supplied dispatch request.
- On receipt of a client supplied dispatch request, the commercial trial organization will select the correct patient supplies and dispatch to the correct site via an approved courier.
- Arrange for disintegration to be carried out on fluoxetine 20mg capsules and destruction also of the placebo capsules.

9.5. Management and accountability of the trial drugs at Site

Prior agreement will be obtained from the central trial pharmacy in Sweden, Apoteket AB, Karolinska University Hospital, Solna, and the responsible research team at each participating site for the drug to be received, stock controlled, stored and temperature monitored in accordance with the SmPC (15 to 25 degrees C) and dispensed on receipt of a prescription and pack details.

9.6. Prescribing and Dispensing of the trial drug

The PI, or physician sub-investigator at the site, will prescribe the allocated trial medication on the patient's medication chart giving the study name and patient id/treatment code (see randomization). The medication should be prescribed as "EFFECTS" trial medication (fluoxetine 20mg / placebo)", one capsule daily, oral (or enteral tube if cannot swallow) for six months. The medication will be dispensed for the first 3 months' supply of study medication (100 capsules). When the patient is discharged from hospital the trial medication will be continued and documented on the discharge summary as well as on the patient's list of ongoing medication. After a little less than 3 months the patient will be assessed for depression, if this is ruled out the trial medication for the last 3 months (100 capsules) will be given or sent to the patient and the prescription will be made in the patient's outpatient medical record at the local trial center.

9.7. Return of unused trial drug

9.7.1. From the patient

After the first 3 months the patients will be asked to return the bottles, whether empty or not, in a freepost envelope to the stroke research nurse at their local trial center.

At 6 months the patients will be asked to bring the trial medication bottles from the last 3 months to the local center at the six months' face-to-face follow up.

9.7.2. From hospitals

A commercial trials organization, Apoteket AB, Karolinska University Hospital Solna will:

- On receipt of a collection request, arrange for the carrier to go into the sites to collect the unused/returned clinical trial supplies.
- At the separate sites also collect the bottles that the patients have sent in or brought with them respectively.
- On receipt of the unused/returned clinical trial supplies, check that the correct number of cartons have been received in compliance with the inventory and inform the client of any damages or discrepancies. This does not include a reconciliation of the enclosed drug product.
- When all unused/returned clinical trial supplies have been returned to the commercial trials organization they will send the material for destruction upon authorization from the client
- Both active trial drug capsules and placebo capsules will be destroyed.
- Send the main coordinating center a Certificate of Destruction.

9.8. DOSING REGIME AND ADMINISTRATION

Patients will be prescribed the study medication (20mg capsule of fluoxetine or placebo capsule) to be taken daily at a time which is likely to maximize their adherence i.e. linked to an activity of daily activity. If the patient is unable to swallow capsules and has a nasogastric (NG) or other enteral feeding tube in place then the capsules may be broken open and the contents put down the enteral feeding tube in accordance with the instructions given in the Svensk Författningshandbok, and according to instructions from Läkemiddelsinformationscentralen at Karolinska University Hospital Solna, telephone +46 (0)8 5177 5342)

9.8.1. PARTICIPANT ADHERENCE

Adherence to the trial medication will be monitored and recorded during the period of hospital admission by the local research team. Once the inpatient has been discharged monitoring of adherence for the remainder of the treatment period will rely on 1) reporting at telephone contacts and 2) self-reporting by the patient or their proxy, and 3) counting any remaining capsules returned to the local trial centre at the mid, and at the end, of the total six months treatment period.

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

- Encourage the randomizing clinician to emphasize the importance of taking the allocated medication regularly.
- Write to the GPs shortly after enrolment to alert them to the patient's participation in the trial, the potential for drug interactions, and asking them to contact the local center team in case of a suspected or diagnosed depression so that the trial team or the GP can treat this in accordance to the protocol or the patient will be treated by a psychiatrist, we will also ask them to inform us of any suspected adverse reactions to the trial medication.
- Telephone the patient at home at 1 and 4 weeks; and at 3 months after enrolment to make a depression assessment, on each occasion reminding the patients of the purpose of the EFFECTS trial and the importance of adhering to the medication if possible. We will provide the patients with the means to feedback (by post, telephone or web) of any concerns which we would respond to directly or, if the patient is in close contact with their GP, via their GP.

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

9.8.2. OVERDOSE

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

If a person was to take a large number of the trial capsules then there is obviously only a 50% chance that the capsules would contain any active ingredient. The SmPC, Appendix 1, and FASS, as well as the SMPC for Fontex® in "Prövarpärmen" highlight that cases of overdose of fluoxetine alone usually have a mild course and that fatalities are extremely rare (Reference list: 'Reference Safety Information'). The information includes details of possible symptoms of overdose and advice regarding its management. The patient should be admitted to hospital for surveillance.

9.8.3. STOPPING THE TRIAL DRUG, and drug metabolism and elimination

Sudden cessation of an SSRI may lead to a withdrawal syndrome characterized by symptoms including headache, anxiety, restlessness, insomnia, headache, tremor and paresthesia. However, of all the SSRIs, fluoxetine has the longest half-life of the SSRIs fluoxetine is mainly metabolized by the CYP 2D6 enzyme mainly in the liver to its active main metabolite norfluoxetine (demethylfluoxetine). The half-life is 4-6 days for fluoxetine and 4-16 days for norfluoxetine. The long half-life leaves the drug in the body for in all 5-6 weeks after termination of the treatment. The elimination is approximately by 60 % via the kidneys. A withdrawal syndrome is hence uncommon with fluoxetine; tapering of the dose (especially from only 20mg OD) is not regarded as necessary. In case of withdrawal symptoms the patient will be advised to contact the local trial center and if any re-start of study treatment is found necessary the same procedure as described “in case lost medication” page 27 will be applied, in case of a general agreement as to this with the MPA the patient might in mild cases be given their remaining capsules from their dispensations with the more than 14 back-up capsules. There will be an individualized prescription for a slower withdrawal of the study-drug under the supervision of the local PI. Any prescription will be noted by the PI in the patient’s outpatient medical record and in the trial medication note. With this method any patient with presumed withdrawal symptoms will be recorded and followed up. We do not expect withdrawal reactions, but if these occur the vast majority should get a sufficient length of prolonged withdrawal by the continued blinded termination of the study-treatment under the control of the PI. In the rare case where the withdrawal symptoms would not seize till the 7 month follow up, or symptoms would take an unusual course any time after ending the ordinary trial treatment at six months, the patient will be referred to a psychiatrist. Under all circumstances no patient will be left with any treatment without specialist control.

9.9. OTHER MEDICATIONS

9.9.1. Permitted Medications:

Diagnosis and treatment of depression during the EFFECTS trial

A new diagnosis of depression, a diagnosis leading to referral for an assessment at the local center, and if needed by a specialist psychiatric assessment, a diagnosis severe enough to require treatment with an antidepressant is a secondary outcome in the trial. Our hypothesis is that new depression will be less commonly diagnosed and treated in the group allocated fluoxetine. We will ascertain cases of depression by:

- Asking about a diagnosis or initiation of an antidepressant during hospital admission or during the first month– this will be recorded on the locally completed discharge form.
- Paying due attention to the patient’s report at the 1 and 4 weeks telephone contacts.
- Investigating the patient for depression at three months.
- Investigating the patient at the 6 months face-to-face follow up; and asking the General practitioner at 12 months.
- Asking the patient (or their proxy) at 6 months; 7 months, and 12 months

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

If a patient in the EFFECTS trial is diagnosed as having depression (or pathological emotionalism) which the responsible clinician judges to be severe enough to justify treatment with antidepressant drugs we would recommend that if possible they should avoid any SSRIs and prescribe

Mirtazepine. Mirtazepine is compatible with fluoxetine (there are no common or important interactions) although since Mirtazepine has some serotonergic activity there is likely to be a slightly greater risk of precipitating a serotonergic syndrome. Mirtazepine is recommended for treatment of depression in patients with physical illness. The clinician might as a non-usual alternative use a tricyclic antidepressant, preferably clomipramine in a low dose. All treatment of emotional reactions should preferably be discussed at least principally with a psychiatrist and for general decisions with the trial psychiatrist.

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

Patients taking the trial drug and another antidepressant should be monitored carefully (e.g. check plasma sodium levels to exclude hyponatremia) to identify any potential interactions. Any change in treatment will be undertaken at the discretion of the PI but must also be reported in the trial documents.

9.9.2. Prohibited Medications

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

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

Also medication with analgesics containing tramadol and migraine medication with sumatriptan should preferably be avoided or closely monitored at the discretion of the PI for any sign of an emergent serotonergic syndrome.

10. STUDY ASSESSMENTS AND DATA COLLECTION

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

10.1. STUDY ASSESSMENT SCHEDULE

Assessment	Days	Weeks/Month(s)					
	2-15	1 week	1 month	3 months	6 months	7 months	12 months
<i>Intervall of time (+/- numbers of days, D)</i>		+/- 3D	+/- 7D	+/- 7D	+/- 14D	+/- 7D	+/- 14D
Local							
Screen of eligibility	X						
Check results of post stroke bloods and mood (MADRS, if ≥ 10 : DSM-IV)	X						
Give PIB to patient and next of kin	X						
Concent	X						
Collect Baseline data at inclusion. NIHSS, MADRS and DSM-IV (depression), MoCA (cognition), NGTA (short aphasia test), EQ5D-5L	X				X		
Randomize and email the study medication number of the allocated dispensed bottle including patient ID	X						
Record treatment code/study no.	X						
Prescribe study medication	X						
Dispense for 3 months of treatment	X						
Complete discharge form	X						
Updated contact details	X				X		X
Local							
Emailnotification of allocation	X						
Letter informing GP of participation	X						
Telephone contact, check adverse event, adherence to medications		X	X				
Face-to-face or telephone: Rule out depression (MADRS/DSM-IV), NGTA, EQ5D-5L, AE/SAE, Patient returns first 3 months' trial medication bottles Dispense trial medications for last 3 months				X			
Check survival		X	X		X		X
6 months face-to-face follow-up							
Patient brings old trial med bottles					X		
Resource use	X	X	X		X		X
Retrieve residual capsules (pill count) After trial ends: reconciliation and destruction.					X		X
Check for emerging post-study treatment depression						X	

Central (blinded)							
Mail questionnaires					X		X
Modified Rankin scale					X		X
Stroke Impact Scale					X		X
Mental health inventory 5					X		X
EQ5D-5L					X		X
Health Questionnaire vitality subscale					X		X

10.2. STUDY SAFETY ASSESSMENTS

Our monitoring system will primarily be aimed at identifying **S**uspected **U**nexpected **S**erious **A**dverse **R**eactions (SUSARS) but also identifying whether the frequency of as well **A**dverse **R**eactions (all Adverse Events will be recorded) and **S**erious **A**dverse **R**eactions is greater than in other populations given fluoxetine and sufficiently common to offset any benefits.

The trial materials given to the patient and their carer will give the most common of the known adverse reactions to fluoxetine (based on the SmPC/FASS) and the information on how to get in contact with a physician at their local centre 24/7/365 in case of any suspected other adverse reaction.

24 Hours' Helpline

Physicians and nurses at the local centers and the patients' GPs or other responsible physician are able to reach the Chief Investigator or delegated colleagues on the **24 Hours EFFECTS Helpline number 073 6637 444**.

Alert of Adverse Reactions

Patients enrolled whilst an inpatient will have a hospital discharge form completed by the local research nurse at the time of discharge from the recruiting center. The data collected will be entered on a secure web based form and the discharge form to ensure that we are alerted to any important **A**dverse **R**eactions, and to provide information concerning adherence, adverse events, non-IMP medications and outcomes.

The local center telephone contacts at 1 and 4 weeks are also aimed at detecting Adverse Reactions for outpatients. Also at 12 weeks after randomization i.e. at the 3 months contact, the local center will specifically ask the patients to report any adverse events or difficulties with the trial medication.

All surviving patients will be followed up at 6 and 12 months after randomization, whether they adhere to their allocated treatment or not. In order to detect **A**dverse **R**eactions between the scheduled follow ups the patient and carers get a phone number to the local center.

The patients' GP, or other responsible physician and the PI will get information about the trial 24h Helpline.

10.3. LOCAL AND CENTRAL FOLLOW UP

About 2 weeks before the 6 and 12 month follow ups are due the local trial center will check that the patient is alive so that they may be approached for follow up. and suggest a time for the face-to-face follow up at the hospital.

The main center will mail the questionnaire to the patient prior to/ at 26 weeks, for the 6 month follow up. . The patient fills in the forms and sends them in a freepost envelope to the main center. If the main center does not get any forms, a reminder goes out. In case of no reply, a research nurse at the main center will contact the patient and make the assessments over the phone. The procedures will be the same at 52 weeks, the 12 months follow up, but without any face-to-face investigation at the local center.

The questionnaire at 26 and 52 weeks aims to capture the primary and secondary outcomes and includes the outcome of any adverse events which have been reported earlier in the follow up. If

the patient has incapacity, the next of kin (proxy) will be asked to complete and return the forms. If the patient is unable to speak Swedish but has been included due to a Swedish speaking next of kin we will ask that they support them in filling out the forms.

Long-term survival

We plan to determine long term survival until the end of the trial for all patients. This will be achieved by the main centre annual check of civil registry via the hospital medical files-system. There is evidence that functional outcome at 6 months post stroke is strongly associated with long-term survival (Bruin 2008). Therefore, if fluoxetine treatment is associated with improvements in functional status at 6 months it would be important to establish whether this translates into longer survival.

11. STATISTICS AND DATA ANALYSIS

11.1. SAMPLE SIZE CALCULATION

We are planning to enroll 1500 patients in the EFFECTS trial with equal number in each trial arm. This will provide 90% power to detect a 5.6% absolute increase in percentage with mRS 0-2 from 27.0% to 32.6% based on an ordinal analysis which is statistically more efficient than an analysis which dichotomizes the mRS (OAST 2007). Data from FOCUS and AFFINITY, the trials with which we share the minimal data set, aim to enroll 3000 + 1600 respectively, in all 4600 which if added to the EFFECTS inclusion will yield 6100 patients and provide 90% power to detect a 4.6% absolute improvement in percentage with mRS 0-2 from 27.0% to 31.6%.

In arriving at the sample sizes account has been taken of the effect sizes seen in the FLAME trial alongside the effects which clinicians, and their patients would find interesting. Since fluoxetine is safe and inexpensive, we seek reliably to detect the moderate, but nonetheless clinically important benefits that might be associated with widespread use of fluoxetine in this population. We will monitor the feasibility of enrolling large numbers of patients into the EFFECTS trial.

The expected outcomes for the placebo group in EFFECTS are based on the distribution of mRS score measured at 6 months after randomization in the CLOTS trials which evaluated graduated compression stockings (CLOTS 2009) (FOCUS trial protocol www.focustrial.org.uk).

Using the ordered categorical data method described by Machin (2008), and discussed at the following address <http://www.childrens-mercy.org/stats/weblog2004/OrdinalLogistic.asp>, an excel sheet built by the FOCUS group calculated the sample size required. As can be seen in the FOCUS protocol the cells which had to be specified to calculate the sample size were: the numbers in each category, power, significance level, 1 or 2 sided and also the common odds ratio.

11.2. PROPOSED ANALYSES

Our primary analyses will retain patients in their original assigned treatment groups, i.e. the basis of Intention-to-Treat (ITT) analyses.

Our primary analysis will compare the mRS at the six month follow up using an ordinal analysis adjusted for any baseline imbalance in those factors included in our minimization algorithm.

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

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

- Survival (Logistic regression)
- EQ5D-5L (HRQOL) to generate utilities
- Direct and Indirect costs from a societal perspective, to estimate cost-effectiveness of treatment with fluoxetine on post-stroke sequelae. The cost-effectiveness will be assessed both at one year and over the cohort lifetime.
- SIS (for each of 9 domains on which the patient scored 0-100)
- MHI 5 (mood)
- Fatigue (Vitality subscale of SF36)
- New diagnosis of depression requiring treatment with antidepressants
- Adverse events
- Adherence to trial medication

Longer term survival will be analyzed with Cox proportional hazards model

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

11.2.1. Pre-defined subgroups

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

- Age (≤ 70 , > 70 yrs)
- Baseline probability of a good outcome on mRS (Counsell 2002) – to see if effects remain constant across the range of stroke severities (< 0.15 vs $0.15-1$ probability of being alive and independent at 6 months)
- Ischaemic vs. hemorrhagic stroke
- Patient who were unable to consent for themselves since this subgroup will allow us to answer the question whether routine use of fluoxetine is likely to benefit patient in whom a formal assessment of mood is difficult or impossible because of communication or cognitive problems.

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

Patients with a motor deficit (i.e. weakness or clumsiness on NIHSS) affecting face, arm or leg.

- Relevant outcomes – SIS – Strength, mobility, hand/arm function

Patients with aphasia based on the NIHSS

- Relevant outcomes – SIS – communication

The face-to-face assessments will be used for additional secondary analyses for benefits in relation to the specific deficits and possible interactions with mood:

- motor function – NIHSS

- speech – NGTA
- cognition – MoCA
- mood – MADRS/DSM IV

A detailed analysis plan will be developed and reported by the chief investigator and one independent, statistician prior to the database being locked at the end of follow up for final analysis. The follow-up is undertaken from the main center and from our experience in the IST-3 trial where our follow-up was 100 %, and by the use of the same methodology as in IST-3 and also in other trials in Edinburgh where we know their follow-up rate to be close to one-hundred percent, we will expect better than 98 % in EFFECTS. The follow-ups on secondary data will be made in line with the CONSORT guidelines which accounts for every patient (Schulz KF et al, 2010). As for secondary analyses patients will be analyzed as per the group they were included in i.e. the original randomization allocation. This is the basis of the definition of each group. The secondary analyses may have missing data. There will be several analyses performed: without accounting for the missing data; with a variety of sensitivity analyses, i.e. based on the ITT-population with imputed outcome from baseline to 6 months, and with imputed outcome from 6 months to 12 months. The sensitivity analyses are used to give the basis for robust conclusions.

In line with our trial design with no interim-analysis, and if no objections from the DMC, we will proceed seamlessly from the feasibility to the main-phase. If no alterations to the trial eligibility have been made the feasibility-phase patients will be included in the analyses.

11.2.2. Cost-utility analysis

Within trial analysis that will compare the resource consumption and costs, and quality of life outcome (utility), of the two treatment arms. The analysis will be conducted on an intention to treat basis (and for the complete case analysis as a sensitivity check). A societal perspective will be adopted for measuring and valuing health service according to the health-economic SHARE system (Malmberg G. personal communication 2012) which will allow comparison to other SHARE-countries.

We will estimate the 3-month, 6-month, and 1-year direct and indirect costs. The direct costs are: transportation to hospital (ambulance or own), inpatient care (days in intensive care unit and in general hospital ward), outpatient care (visits to neurologist, other medical specialist, general practitioner, speech therapist, other), rehabilitation (visits to physiotherapist, other rehabilitation specialist), consumption of other prescribed and over the counter medication, nurse home visits, home care visits, hours informal caregivers spend for the care of the patient, home alterations to improve mobility/other. The indirect costs refer to the hours lost from work for the stroke patient (if still working), leisure time lost for the patient (working and non-working stroke patients), and disability pension. In the case of missing cost information, multiple imputation methods will be used to address the missing values. Whenever it is possible, data from national registry will be used instead of patient reported data.

Self-reported quality of life will during the pilot phase, measured at baseline, 1 week, patient or proxy), 4 weeks 3 moths, 6 months, and at 12 months of follow up will be measured using the EuroQoL 5 Dimensions (EQ5D-5L) scale. In the main phase, EQ5D will be measured at inclusion, at 6 and 12 months follow-up. Then utility score, between zero and one, will be estimated through an algorithm especially designed to connect the individual patient responses with relevant population weights. We also plan to validate the EQ5D-5L instrument by checking its concordance with the quality of life score obtained through the modified Rankin scale. Finally the effectiveness measure that will be used for comparison purposes, the quality adjusted life years (QALYs), will be estimated by multiplying the relevant time parameter of the comparison with the estimated utility scores. As with costs, missing information will be imputed using multiple imputation

methods, according to previously validated methods for handling missing EQ5D information in a clinical trial/study.

The comparison of costs and effects (QALYs) between the treatment arm will be conducted for the period of the clinical trial, as well as by adopting a lifetime perspective, where costs and QALYs will be extrapolated beyond the duration of the trial over the expected lifetime of patients. Standard statistical regressions will be used in order to calculate the expected lifetime costs and QALYs.

12. ADVERSE EVENTS

The Principle Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below (12.5). Also the PI must report all SAE/SAR and SUSARS within time-frames given.

12.1. DEFINITIONS

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

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

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

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

- results in death;
- is life threatening* (i.e. the participant was at risk of death at the time of the event)
- requires inpatient hospitalization or prolongation of existing inpatient hospitalization
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect.

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

Any hospitalization that was planned prior to randomization will not meet SAE criteria. Any hospitalization that is planned post randomization will meet the SAE criteria.

It is the principal investigator's responsibility to decide whether the event was *related* (resulted from administration of any of the research procedures) or *unexpected* (type of event not listed in the protocol as an expected occurrence; i.e. not in the IB and in EFFECTS not listed in SmPC or FASS).

12.2. Assessment of AEs

12.2.1. Assessment of Seriousness

Each AE must be assessed for **seriousness**, **causality** (related, or not, to the IMP), **severity** and **expectedness** by the Principle Investigator or another suitably qualified physician/ Investigator at the local research team who is trained in recording and reporting AEs and who has been delegated this role. For randomized double blind studies, AEs will be assessed as though the trial participant was taking the IMP. All AEs/ARs will be accounted for.

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

12.2.2. Assessment of causality

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

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

Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship makes it possible that the AE has a causal relationship to the study drug. Alternative causes such as natural history of the underlying disease, other risk actors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

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

12.2.3. Assessment of Severity

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

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

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

Severe: an event that prevents normal everyday activities. The term 'severe' used to describe the intensity of an event should not be confused with the term 'serious', as defined in section 12.1, which is a regulatory definition based on trial participant/event outcome action criteria. For example, a headache may be severe but not serious, while a minor stroke may be serious but is not severe.

12.2.4. Assessment of Expectedness

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

- **Expected:** the reaction is consistent with the toxicity of the study drug listed in the SmPC
- **Unexpected:** the reaction is not consistent with the toxicity listed in the SmPC.

12.3. FLUOXETINE

Fluoxetine is a well-established drug which has been used for more than 20 years in the treatment of depression, and other related problems and has a well-established safety profile. It has been used to treat depression and emotionalism in many thousands of patients worldwide. The following events are expected in this patient population and will NOT be reported to the main centre within 24 hours, even in situations where these expected events fulfill the criteria of serious (as defined in section) of the trial protocol.

12.3.1. Known Side Effects of fluoxetine

The Summary of Products Characteristics dated 2012-03-18 (Läkemedelsverket, Fontex®) records that fluoxetine can cause a variety of side-effects. The patient may present with:

- Fever and asthenia
- Frequent side-effects to the digestive system (gastrointestinal tract) include nausea, diarrhea, vomiting, dyspepsia, abdominal pain, constipation, dry mouth and appetite loss.
- Less frequent is abnormal liver function.
- The nervous system responses are shown as headache; insomnia, drowsiness; dizziness; dyskinesia; nervousness; anxiety; tremor; fatigue; asthenia; seizures; convulsions and hypomania or mania behavior may be evident; sexual dysfunction with decreased libido and delayed orgasm may be experienced; voluntary movement impairment; movement disorders including worsening of pre-existing movement disorders and neuroleptic malignant syndrome-like events may be experienced. Hyponatremia may develop (usually in the elderly), which may be due to inappropriate antidiuretic hormone secretion. This condition should be considered in all patients who develop drowsiness, confusion or convulsions while taking fluoxetine.
- Pulmonary events have rarely been reported, including inflammatory processes of varying histopathology and/or fibrosis. Respiratory system responses are shown as dyspnoea, which may be the only preceding symptom, and pharyngitis.
- Hypersensitivity reactions, with the development of skin rashes, angioneurotic oedema, urticaria and other allergic reactions have been reported. The development of rashes may be the first symptoms of serious systemic reactions, possibly related to vasculitis.
- Patients may experience sweating, arthralgia, myalgia, serum sickness, anaphylactoid reactions, weight loss and hair loss.
- Fluoxetine may cause changes in blood sugar. Also, abnormal liver function tests have been reported.
- Undesirable effects constituting the symptoms of Serotonin Syndrome ('serotoninergt syndrome') consist of hyperthermia, muscle rigidity, myoclonus, instability of various autonomic nervous system functions such as cardiovascular, sweating, respiratory and/or gastrointestinal effects and in addition, changes in mental status which may, in severe or untreated cases, progress to delirium, coma and even death.

12.3.2. Other Undesirable Effects Reported but no causal relationship established

A number of other undesirable effects have been reported, however no causal relationship with Fluoxetine has been established. These include aplastic anemia, thrombocytopenia, thrombocytopenic purpura, gastrointestinal hemorrhage, hyperprolactinemia, immune-related hemolytic anemia, cerebrovascular accident, confusion, ecchymosis, eosinophilic pneumonia, pancreatitis, pancytopenia, vaginal bleeding after drug withdrawal, suicidal ideation and violent behavior.

Cases of suicidal ideation and suicidal behaviors have been reported during fluoxetine therapy or early after treatment discontinuation (see section 4.4 of the SmPC, Produktresumé).

12.3.3. Class effects

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

The frequency of some adverse events may be affected by the fluoxetine. A cohort study (Coupland et al 2011) 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 SSRIs were associated with significantly higher rates of:

- all-cause mortality (adjusted hazard ratio 1.54; 95% confidence interval 1.48 -1.59)
- stroke/TIA (1.17; 1.10-1.26)
- myocardial infarction (1.15; 1.04 -1.27)
- upper gastrointestinal bleeding (1.22; 1.07- 1.40)
- serious falls (1.66; 1.58 -1.73)
- serious fractures (1.58; 1.48 -1.68)
- epilepsy/seizures (1.83; 1.49 - 2.26)
- attempted suicide/self-harm (2.16; 1.71 - 2.71)
- hyponatremia (1.52; 1.33 to 1.75)

12.4. Pre-specified outcomes

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

Stroke is a serious medical condition where medical complications are common and poor outcomes frequent. About 10-20% of hospitalized patients would be expected to die in the first month after a stroke and another 10% by the end of the first year. Up to a third will develop a chest or urinary tract infection whilst in hospital; some 5% will develop clinically apparent venous thromboembolism, epileptic seizures or gastrointestinal bleeding. Many patients fall, and some sustain injury.

Therefore, adverse events many of which would be categorized as serious (as per the definitions in section 10.1) are likely to be frequent in the trial.

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

12.5. ADVERSE EVENT REPORTING FOR THIS TRIAL

12.5.1. You should NOT report to the trial sponsor at the main Trial Co-ordinating Center:

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

- Chest infections
- Urinary infections
- Other infections including those of soft tissues
- Renal dysfunction
- Painful shoulder syndromes
- Pressure sores

- Spasticity or contractures
- Any other known complications of stroke

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

12.5.2. You SHOULD report to the Trial Co-ordinating Centre

The following Adverse Events should be reported to the Trial Co-ordinating Centre on the discharge form. These events will also be collected during the 6 months of follow up when the patient is taking the medication providing they meet the criteria of a Serious Adverse Event as defined in section 12.1.

- all-cause mortality
- stroke/TIA
- myocardial infarction
- upper gastrointestinal bleeding
- serious falls
- serious fractures
- epilepsy/seizures
- attempted suicide/self-harm
- hyponatremia

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

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

12.5.3. You MUST report to the Trial Sponsor

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

12.5.4. Reporting SAEs/SARs/SUSARs to the Trial Sponsor

Once the Principal Investigator becomes aware that any 'reportable' SAE/SUSAR has occurred in a study participant, they must report the information to the sponsor at the trial main centre who will report to Medical Products Agency within 24 hours. The SAE/SUSAR form must be completed as thoroughly as possible with all available details of the event, signed by the Investigator or designee. If the Investigator does not have all information regarding an SAE/SUSAR, they should not wait for this additional information before notifying sponsor. The form can be updated when the additional information is received.

The SAE/SUSAR report must provide an assessment of causality and expectedness at the time of the initial report to sponsor according to Sections 12.2.2, Assessment of Causality and 12.2.4, Assessment of Expectedness.

The SAE form should be transmitted by fax to the sponsor on 08-755 5951. SUSAR should be reported to the Help-line (073- 663 74 44) within 24 h. Where missing information has not been sent to sponsor after an initial report, the MPA will contact the Investigator and request the missing information until this is supplied,

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

12.6. SPONSOR REGULATORY REPORTING REQUIREMENTS

The sponsor is responsible for Pharmacovigilance reporting to the MPA. The sponsor has a legal responsibility to notify the regulatory competent authority and the regional ethics committee that approved the trial (to be further discussed with MREC Secretary). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after sponsor is first aware of the reaction. SUSAR reports from the sponsor to the MPA will be by letter.

The Trial Co-ordinating Centre will inform Investigators at participating sites of all SUSARs and any other arising safety information. Safety information sent to the trial co-ordinating centre must be forwarded to MPA.

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

12.7. Need Advice?

Advice for investigators on reporting of adverse events will be available in the trial manual, on the trial website, and via the 24 hour telephone Helpline (073 6637 444).

12.8. Emergency Unblinding Procedures for this study

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

In the event of a SUSAR, the sponsor will have the facility to allow them to unblind the patient prior to the expedited reporting to the MREC and the MPA.

13. PREGNANCY

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

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

14. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

14.1. TRIAL MANAGEMENT GROUP

Trial Management Group (TMC) consists of Dr Erik Lundström (Chief Investigator), Eva Isaksson (Trial Manager), Trial Manager Assistant (TBA), Per Wester, Per Näsman (Lead Trial Statistician) and Dr Björn Mårtensson (Psychiatrist).

14.2. Trial Steering committee

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

Trial Steering Committee will meet annually and the members will be made up of but not limited to the following:

1. Professor Katharina Stibrant Sunnerhagen (Independent Chairman)
2. Lead Clinical Trial Advisor: Professor em Björn Beermann, formerly at Swedish Medical Product Agency
3. Chief Investigator: Dr Erik Lundström
4. Trial Manager: Eva Isaksson
5. Professor Bo Norrving
6. Professor Per Wester
7. Professor Håkan Wallén
8. Professor Jörgen Borg,
9. Lead Statistician: Senior statistician Per Näsman
10. Lead Psychiatry and antidepressant Advisor: Dr Björn Mårtensson, MD, PhD
11. Ass. Professor Christina Sjöstrand
12. Co-Chief Investigators of FOCUS: Professor Gillian Mead, Professor Martin Dennis
13. Co-Chief Investigators of AFFINITY: Professor Maree Hackett, Professor Graeme Hankey
14. Lay representative: TBA
15. Funding representative: As requested and in agreement with Karolinska Institutet

14.3. Advisory Board

Professor em Björn Beermann, formerly at Swedish Medical Product Agency (Lead Clinical Trial Advisor)

Professor Eero Castrén; Helsinki University (Pre-clinical scientific advisor)

Professor em Marie Åsberg (Psychiatry advisor)

Ass Professor Magnus von Arbin and Dr Ann Charlotte Laska MD, PhD (senior stroke specialists)

Dr Anders von Heijne; and Dr Evaldas Laurencikas, MD, PhD (Specialists Neuroradiology)

Påvel Lindberg, PhD (Neuroradiology advisor), Université Descartes, Paris and KI

The Principle Investigators at each participating center will be part of one of these constellations

14.4. Planned sub-studies on mechanism and hemostasis and inflammatory parameters

Within the EFFECTS there are plans for sub-studies on the underlying mechanisms with professor Jörgen Borg as co-chief investigator, and Håkan Wallén as co-chief investigator in a sub-study on hemostasis and inflammation. These two studies must be done in collaboration with Chief Investigator.

14.5. Data Monitoring Committee (DMC)

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

The terms of reference of the Data Monitoring Committee, the DMC Charter and the names and contact details will be agreed at the first meeting of the DMC.

The Chairs of the DMCs of EFFECTS, FOCUS, and AFFINITY will communicate to share any concerns about the accruing data and will share data if indicated. Therefore the DMC will potentially have access to all available information when making its recommendations. This aims to maximize patient safety.

The DMC of EFFECTS is:

Chair: Professor Kjell Asplund; member: Professor Andreas Terént, statistician: Anders Ljungström.

14.6. TRIAL CO-ORDINATING CENTRE (TCC)

The TCC is responsible for all aspects of the management of the EFFECTS trial; the TCC is located at the Stroke Research Centre at Karolinska Institutet Danderyd Hospital. Responsibilities include: Regulatory Submissions and compliance; Financial Management; Monitoring of Sites; Training; Patient Information and Communication; Endpoint Assessment; Data Collection Systems and Data Management; IMP Management; Statistical Analysis; Reports and Publications and Archiving of the Trial Master File (TMF) in accordance with funder and sponsor requirements.

14.7. INSPECTION OF RECORDS

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

14.8. RISK ASSESSMENT

An independent risk assessment of the trial and its procedures will be carried out by a Sponsor's Clinical Trials Monitor (TBA) to determine the level of monitoring. An independent risk assessment

will also be carried out by the Sponsor's Clinical Trials Monitor - Quality Assurance Group (to be defined) to determine if an audit should be performed before/during/after the study and if so, at what locations and at what frequency.

14.9. STUDY MONITORING

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

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

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

14.10. Monitoring plan:

The centre: to assess activity and correct application of eligibility criteria, a screening log will be maintained from the start-up visit; any systematic problems may be identified and dealt with. All trial staff documentation including CVs, certificates of GCP-training within the last two years, and the delegation log will be collected at the site initiation visit, please see page 49 “Principal Investigator Documentation”. The delegation log will be entered into the IT-system and additions to the log will be made by the PI and entered into the IT-system.

The first randomized patient at each centre: will initiate a visit and full monitoring. This includes full source data verification on site: control of patient identity versus the medical file; check of correctness of the informed consent form versus notes on consent and randomization in the medical file; study-drug accountability. All use of trial forms including the safety documentation is assessed against the medical file/s; this also reveals any mistakes in filing data into the CRF.

For all patients: Check of patient id; informed consent form; and trial medication accountability will be checked by source data verification on site as will the PI's judgment of adverse events and their further classification and reporting is also assessed.

For 10 % of the patients: All data will be monitored by source data verification on site including Efficacy and Risk Assessment which includes adherence to the Protocol and patient safety.

14.10.1. Archiving of centre data

All trial related and source documents should be archived for ten years following the end of the trial. The costs for this must be discussed and agreed locally by each R&D department as part of the R&D approval process. There may instead be central archiving and only one file left at the local centre with a list of recruited patients and the information as to the location of the storage of trial related and source documents.

14.10.2. Archiving of central data

All trial related documents will be archived for 10 years in accordance with the Sponsor archiving policy unless an alternative longer archiving period is specified by the funder.

15. GOOD CLINICAL PRACTICE

15.1. ETHICAL CONDUCT

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

A favorable ethical opinion will be obtained from the MREC at Karolinska Institutet and local R&D/hospital/department approval will be obtained prior to commencement of the study.

15.2. REGULATORY COMPLIANCE

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

15.3. PRINCIPAL INVESTIGATOR RESPONSIBILITIES

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

15.3.1. Confirming patient eligibility

Although a research nurse may be delegated the responsibility for identifying suitable patients, obtaining consent (see section 5.2) and prepare the randomization of the patient, the PI or physician sub-investigator must confirm in writing in the medical records details on obtaining the informed written consent and that the patient fulfils the eligibility criteria.

15.3.2. Study Site Staff

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

15.3.3. Data Recording

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

15.3.4. Principal Investigator Documentation

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

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

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

15.3.5. GCP Training

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

15.3.6. Confidentiality

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

15.3.7. Data Protection

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

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

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

15.3.8. Follow up

The PI is responsible for the discharge follow up of participants until hospital discharge or death (whichever occurs first) or at around 1 month. In exceptional circumstances, where central follow up has failed, the PI may be requested by the TCC to collect follow up data at 6 and/or 12 months.

16. STUDY CONDUCT RESPONSIBILITIES

16.1. PROTOCOL AMENDMENTS

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

Amendments to the protocol must be submitted in writing to the Multicentre Ethics Committee at Karolinska Institutet, the MPA and if relevant to the local R&D for approval prior to participants being enrolled into an amended protocol. Every center must have the latest version of the protocol in their Investigator Site File. Amendment relating to the addition of centers in the study do not need to be sent out to all centers as a protocol amendment. This is communicated in connection with major protocol changes and electronically via the newsletter and on the study website (www.effects.se).

16.2. PROTOCOL VIOLATIONS AND DEVIATIONS

Principal Investigators should not implement any deviation from the protocol without agreement from the Chief Investigator who will achieve appropriate Ethics and MPA, and in relevant cases R&D, approval except where necessary to eliminate an immediate hazard to trial participants.

In the event that an Investigator needs to deviate from the protocol, the nature of and reasons for the deviation should be recorded in the CRF. If this necessitates a subsequent protocol amendment, this should be submitted to the MREC, MPA and if relevant local R&D for review and approval if appropriate.

16.3. STUDY RECORD RETENTION

Each participating centre will be responsible for ensuring that all essential documentation are retained and archived; the archiving will be undertaken in collaboration with the main centre.

16.4. SERIOUS BREACH REQUIREMENTS

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

- (a) The safety or physical or mental integrity of the participants of the trial; or
- b) The scientific value of the trial.

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

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

16.5. END OF STUDY

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

The Chief Investigators and/or the Trial Steering Committee have the right at any time to terminate the study for clinical or administrative reasons.

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

A summary report of the study will be provided to the MPA within 1 year of the end of the study.

16.6. CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

The IMP will not be continued beyond the 6 month treatment period in the EFFECTS trial. The patients local GP or physician may choose to treat the patients with fluoxetine after the patient has stopped taking the IMP. An exception occurs if the patient develops withdrawal symptoms in which case the patient will be reinitiated on the study drug (same procedure as in lost medication, section 6, page 27, also described in detail in the end of section 9.8.3 on page 32).

16.7. INSURANCE AND INDEMNITY

The sponsor is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the sponsor's responsibilities:

- The Protocol has been designed by the Chief Investigator and further researchers. The protocol must approved by the MREC and the MPA.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the Sites concerned but each site is covered by Patientförsäkringen. The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

COLLABORATION

The EFFECTS trial is one in a family of three trials each with own statistical power. The other two are the FOCUS – UK trial and the AFFINITY – Australia trial. The trials share the design and primary effect variables, i.e. minimal data set. In this way each trial can add specific issues but the core will be the same. This means that we will not only be able to give the internal validity of each trial but also the external validity, the generalizability. We will also undertake a metaanalysis. Further this set up of national trials will get power also for subgroup analyses and secondary outcome analyses. We will publish all common data in joint publications, as well the trial protocol, the statistical analysis plan, the main findings etc. We can also publish our separate findings from each trial. We have a highly constructive collaboration and are members in each others Steering Committees. Our independent chairmen of our respective DMC will be able to make joint principle decisions if needed. We have no financial bonds and each trial has its own approvals from Ethics committees and regulatory bodies, and separate grants.

This set up of national trials has been given credit in the journal Trials.

17. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

17.1. AUTHORSHIP POLICY

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

17.2. PUBLICATION

GENERAL PUBLICATION PRINCIPLE

After the feasibility phase the protocol will most certainly have some amendments to be submitted to the regulatory and grant giving bodies. The final protocol will thereafter be published as the first in a series of methodological publications to give full transparency.

All relevant publications will be made by the three trials together in order to gain the impact of the collaboration. Findings outside the core design and minimal data set including possible sub-studies may be published by the separate trial.

When the trial is towards its end, a comprehensive discussion will be held with the trial lead and further expert statisticians. In agreement with the Steering Committee the Statistical Analysis Plan will be finalized and secured for publishing before the breaking of the randomization code. When data have been analyzed and results published we may in due time make data public.

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

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

18. TRIAL ORGANIZATION

Co-ordinating centre (for all information and queries)

EFFECTS Co-ordinating Centre, Karolinska Institutet, Department of Clinical Sciences Danderyd Hospital. email: eva.isaksson@ds.se, telephone: 08 123 5 7693,; 08 755 5951; website <http://www.effects.se> , 24 Hour Helpline 073 6637 444.

19. TIMELINES

Start up /Feasibility phase: 2014-2015

Main phase: 2015-2018

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