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Authors' contributions in the writing committee
Associate Professor Erik Lundström (Neurologist, Uppsala University, Sweden) was the Chief investigator, participated in the steering committee, was involved in the design of the trial, and collected, verified, and analysed data, and wrote first draft the manuscript.

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Professor Bo Norrving (Neurology, Lund University) was involved in the design of the trial and is a member of the steering committee.

Professor Martin Dennis (Stroke physician, University of Edinburgh, UK), Professor Gillian Mead (Stroke physician/geriatrician, University of Edinburgh, UK), Professor Graeme J Hankey (Neurologist, University of Western Australia) and Professor Maree Hackett (Psychologist, University of Sydney, Australia) were involved in the trial design, affiliated to the Steering Committee and analysed data.

All members of the writing committee have refining the study protocol, commented on the analyses and drafts and seen and approved the final version of the manuscript.

Full protocol
The full protocol is available at EFFECTS homepage: http://www.effects.se/english/protocol-and-ethics.

Inclusion criteria for EFFECTS

- Age ≥ 18 years.
- Informed consent. Informed consent was only obtained from a patient who according to the trial investigator was mentally capable of decision-making and who, after having received information and got answers to their questions, wanted to participate in the trial.
- Brain imaging compatible with intracerebral haemorrhage or ischaemic stroke.
- Randomisation performed between two and 15 days after stroke onset.
- Persisting focal neurological deficit present at the time of randomisation severe enough to warrant treatment from the physicians and the patient's perspective.

Exclusion criteria for EFFECTS

- Subarachnoid haemorrhage, except where secondary to a primary intracerebral haemorrhage.
- Unlikely to be available for follow up for the next 12 months e.g. no fixed home address.
- Unable to speak Swedish and no close family member available to help with follow up forms.
- Other life-threatening illness (e.g. advanced cancer) that would 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 micromolar/L)
- Pregnant or breastfeeding, women of childbearing age not taking contraception. Minimum contraception is an oral contraceptive. A human chorionic gonadotropin blood test is to be made prior randomisation and after the end of trial medication.
- Previous drug overdose or attempted suicide.
- Already enrolled into a Clinical Trial of Investigational Medicinal Products.
- Current or recent (within the last month) depression requiring treatment with a Selective Serotonin. Reuptake Inhibitor (SSRI) antidepressant.
- Patients who are unable give consent themselves.
- Current use of medications which have serious interactions with fluoxetine.
- Use of any mono-amino-oxidase inhibitor during the last five weeks.
- Fluoxetine in combination with metoprolol used in cardiac failure New York Heart Association Grade III B–IV.

Caution, but not exclusion criteria
- Caution with the concomitant use of serotonergic analgesics containing e.g. tramadol, and anti-migraine medication e.g. sumatriptan.
- There should also be an awareness of a possibly existing interaction between SSRIs and non-steroidal anti-inflammatory drugs, manifested as an upper gastrointestinal bleeding in very rare cases.
- At higher doses of metoprolol used in heart failure indication, one should be vigilant of the interaction and early after enrolment monitor the patient with clinical monitoring including electrocardiogram.

Co-enrolment
Co-enrolment in EFFECTS and the TIMING-study was allowed. The intervention in TIMING is early versus delayed start of direct oral anticoagulant in patients with acute stroke and atrial fibrillation. Thus, all patients would receive direct oral anticoagulant either < 5 days or 5-10 days from the acute stroke.

Consent
The study personnel identified potentially eligible patients while the patient was in the acute stroke unit, geriatric rehabilitation or neurorehabilitation unit. After assessing the criteria, the Principal Investigator or sub-investigator (in either case a physician) was responsible for assessing eligibility, giving information, ensuring informed consent and obtaining the consent form, signed and dated by all parties.

Information was first given orally and then complemented by the patient's and information booklet. It should be emphasised that the participant could withdraw their consent to participate at any time without explanation and that this would not lead to any loss of benefits or loss of any measures to which they otherwise would be entitled.

The participant was given time to ask questions and this was typically included the day after the information was given.

According to Swedish legislation, the patient must consent to be part of a study. All patients provided written informed consent before randomisation. Consent from relatives was not accepted.

Patients with writing and communication problems

If a patient was unable to sign the informed consent form due to paresis, but capable of expressing oral consent, it was possible for a next of kin to sign the form, certifying as a witness that the patient would like to participate. Similarly, it was possible to include a patient with communication difficulties by them expressing their willingness by e.g. nodding. The relative witnessed the consent and signed confirming that they had endorsed the process. Essential information about the trial, the consent procedure, trial ID and treatment ID, including who to contact if unblinding was necessary was documented in the medical records. The participant received a copy of the informed consent form, and the original was filed with the patient's case report form.

Depression at inclusion

If a depression was suspected at inclusion, a medical doctor performed a psychiatric evaluation according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (1) for major depression. If the DSM-IV criteria were fulfilled, the patient was graded the depression with the Montgomery-Åsberg Depression Rating Scale (MADRS) (2). A total score > 9 on the MADRS at inclusion was regarded as a suspected depression (3,4).

The six simple variable model

The six simple model (SSV) (5) included six variables, four at the onset and two prior to the stroke. Onset variables were: age; ability to walk unassisted; ability to talk; and whether confusion is present or not. The two variables before stroke were whether the patient was independent and living alone. The SSV model used the following variables and definitions, captured at randomisation:

1. Age in years to 2 decimal places.
2. Independent before stroke onset. A *yes/no* variable. We asked: "Did the patient require assistance from anyone to undertake activities of daily living (e.g. walking, showering, dressing, feeding, toileting)?" If the answer was *no*, the patient was judged independent.
3. Living arrangements before stroke. We asked about the living arrangement before stroke. One alternative was *living alone*, the other alternatives were *living with someone*, *institutional living*, and *other*.
4. Able to lift both arms off bed. Question at the randomisation form; a *yes/no* variable.
5. Able to walk (even with a walking aid) but without the help of another person? Question at the randomisation form; a *yes/no* variable.
6. Able to talk and not confused, correspond to Glasgow Coma Scale verbal score = 5 (i.e. oriented); a *yes/no* variable. Coded as *no* when any of the below (a – d) conditions were met:
    a. National Institutes of Health Stroke Scale (NIHSS) (6) item 1b (Level of consciousness question) = 1 or 2, or
    b. NIHSS item 1c (Level of consciousness command) = 1 or 2, or
    c. NIHSS item 9 (Language) = 2 or 3, or
    d. NIHSS item 10 (Dysarthria) = 2.

Outcomes

Although we acknowledge that there is no such thing as a perfect stroke outcome scale, we chose scales and adverse events that capture relevant problems after stroke, and that we judged to be relevant both for patient and society.

Why did we select the modified Ranking Scale (7) (mRS) as the primary outcome? The mRS has several strengths: it captures the whole range of outcome – from no symptoms to death – its categories are quite easily understood by both clinicians and patients, its grading correlate with infarct volume, and a single-point change of the mRS is regarded as clinically relevant (8).

Although, the mRS is the most common functional measure of stroke, and has been the primary or coprimary outcome in most large-scale stroke trials (9), it does not encapsulates the whole range of problems seen after stroke. Therefore, we added well-tested, simple and reliable scales that measure relevant post-stroke problems, e.g. quality of life, anxiety, and fatigue.

We added the Stroke Impact Scale (10–12) (SIS) because it is a stroke-specific, comprehensive, health status measure. The scale was developed with input from both patients and caregivers and includes eight domains (strength, hand function, Activities of Daily Living (ADL)/Instrumental Activities of Daily Living (IADL), mobility, communication, emotion, memory and thinking, participation) from across the full impairment-participation continuum. 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 (11,12).

Moreover, it was important that it would be possible to collect data via mail or telephone, for future pooling with our sister trials FOCUS and AFFINITY.

In EFFECTS, we were able to add instruments (compared to FOCUS and AFFINITY) at 3 and 6 months since we did a face-to-face follow-up. We opted for National Institutes of Health Stroke Scale (6) (NIHSS) for stroke severity/change during the course); Montreal Cognitive Assessment (13) (MoCA) for cognition; Montgomery-Åsberg Depression Rating Scale (MADRS) for depression; the amount of rehabilitation (e.g. physiotherapy, occupational, speech and language therapy and neuropsychology and own training) at 1 week, 1 month, 3 months, and 6 months; and Saltin-Grimby Physical Activity Level Scale (14,15) (SGPALS) for physical activity.

Why did we choose 6 months as the time for the primary outcome?
In the Copenhagen Stroke study (16) functional recovery – measured by the Barthel Index – was achieved within two months for the patients with mild strokes, and five months for patients with the most severe strokes. Currently, we do not know when the optimal timing for intervention occurs. Rapid changes occur during the first months (17), and spontaneous recovery seems to reach a plateau at 6 months for most patients. A 3-month follow-up could reduce observed treatment effect. Conversely, longer term follow-up can lead to loss of apparent affect as benefits may be eroded by recurrent events.

Given all the above, we chose the 6-month time frame as a relevant compromise for our primary outcome. Finally, we have a 12-month follow-up in, which makes it possible for us to judge whether possible differences remain.

How the outcomes were collected – Flow diagram and Study Assessment Schedule
Outcomes were collected in three ways: centrally via mailed questionnaire or interview over the telephone, locally with face-to-face follow-up (sometimes telephone), and through the national registry. **Supplementary Figure a** is a Flow Diagram for EFFECTS. For reasons space, we have divided the Study Assessment Schedule in two tables (**Supplementary Table a** and **Supplementare Table b**). In EFFECTS, the date of stroke was defined as Day 0. We allowed randomisation between day two and 15.

Although informing and randomising was permitted on the same day, we soon noticed that it was more successful to wait 6 to 12 hours between information and randomisation. This allowed the patient time to digest the information and discuss with next of kin.

Identify patient with stroke at a Stroke Unit or a Rehabilitation Unit

↓

Check eligibility

↓

Consent

↓

Collect baseline data

↓

Randomise

↙ ↘

Fluoxetine 20 mg for *6 months*   Placebo for *6 months*

↓   ↓

Discharge form

Telephone follow-up by *local* centre **at 1 week and 4 weeks**.
Retention in the study, adherence, safety outcome, adverse events and physical activity.

↓   ↓

3 months follow-up
Local: Face-to-face Secondary outcomes including physical activity.
Assessment of depression using DSM-IV criteria. MADRS if diagnosis of depression.

Patient returns the bottles from the first 3 months and gets a new bottle of trial medication.
Check for retention in the study, adherence, safety outcomes and adverse event

↓   ↓

6 months follow-up
Central: modified Rankin scale, and secondary outcomes, by questionnaire and/or telephone
Local: Face-to face, secondary outcomes, physical activity, adherence, safety outcomes,
and advere events

↓   ↓

7 months follow-up
Local: Telephone contact to ascertain patients have not developed a depression
after termination of trial medication

↓   ↓

12 months follow-up
Central: modified Rankin scale, and secondary outcomes, by questionnaire and/or telephone

↓   ↓

Long-term follow-up
Central: Patients' long-term morbidity and mortality as well as
health economic data via local center's medical records and
national registres in Sweden

Supplementary Figure a. Flow Diagram for EFFECTS. Patients were identified at an acute stroke unit or at a rehabilitation unit. Patients received oral and written information and had to give consent before randomisation. The date of the stroke was Day 0. Randomisation was performed between day two and 15. The diagram illustrate the different assessments. We used the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1) criteria for major depression. If the DSM-IV criteria were fulfilled, we graded the depression using the Montgomery-Åsberg Depression Rating Scale (MADRS) (2).

	Screening, consent and randomisation	Follow-up	
	2 to 15 days	1 week	4 weeks
Allowed interval (± numbers of days, D)		± 3 D	± 7 D

Local centre

Screen of eligibility	x		
Check results of post stroke depression (DSM-IV, MADRS)	x		
Give PIB to patient and next of kin	x		
Consent	x		
Collect Baseline data at inclusion:			
NIHSS, MADRS and DSM-IV (depression), MoCA (cognition), EQ5D-5L			
Randomise patient	x		
Record treatment code/study number	x		
Prescribe study medication	x		
Dispense for 3 months of treatment	x		
Complete discharge form	x		
Email notification of allocation	x		
Letter informing GP of participation	x		
Telephone contact, check adverse event, adherence to medications, physical activity		x	x

Supplementary Table a. Study Assessment Schedule (Part 1/2). Day 0 = day of stroke onset.
An automatic mail including study medication number, allocated dispensed bottle, the EFFECTS trial ID was generated at randomisation and sent to local centre's PI as well as the co-ordinating centre. DSM-IV=Diagnostic and Statistical Manual of Mental Disorders criteria for major depression (1); MADRS=Montgomery-Åsberg Depression Rating Scale (2).; PIB=Patient Information Booklet; NIHSS=National Institutes of Health Stroke Scale (6); MoCA=Montreal Cognitive Assessment (13); EQ5D-5L=EuroQoL Questionnaire for health-related Quality of Life (18).

| | Follow-up | | | |
Time	3 months	6 months	7 months	12 months
Allowed interval (± numbers of days, D)	± 7 D	± 14 D	± 7 D	± 14 D

Local

Face-to-face follow-up. Rule out depression (DSM-IV/MADRS); EQ5D-5L; adherence; safety outcome, adverse events (AE/SAE), physical activity (SGPALS). Patient returns first 3-month trial medication bottles. Capsule count. Dispense trial medications for last three months.	x			
Adherence Rule out depression (DSM-IV/MADRS), EQ5D-5L, Physical Activity, Safety Outcome, Adverse Events (AE/SAE). Patient brings old trial med bottles. Capsule count.		x		
Check for emerging post-study treatment depression.			x	

Central

Mail or telephone follow-up. An 11-page questionnaire including small modified Rankin scale questionnaire (smRSq); Stroke Impact Scale; Mental health inventory 5; EQ5D-5L; Health Questionnaire vitality subscale were sent to the patients 2-3 weeks before the planned follow-up.		x		x

Supplementary Table b. Study Assessment Scale (Part 2/2). DSM-IV=Diagnostic and Statistical Manual of Mental Disorders criteria for major depression (1); MADRS=Montgomery-Åsberg Depression Rating Scale (2); NIHSS National Institutes of Health Stroke Scale (6); MoCA Montreal Cognitive Assessment (13); EQ5D-5L=EuroQoL Questionnaire for health-related Quality of Life (18). Physical Activity is coded into Saltin-Grimby Physical Activity Level Scale (SGPALS) 4 levels (14,15).

Primary outcome

The primary outcome was functional status, measured with the modified Rankin scale (7) at 6-month follow-up. We used the simple modified Rankin scale questionnaire (smRSq) (19–21) delivered by postal questionnaire or via interview over the telephone to derivate the modified Rankin scale. The smRSq consists of five questions, and each question can be answered with a yes or a no. Based on the response, it is possible to code the answer into mRS 0–5 according to an algorithm (**Supplementary Figure b**).
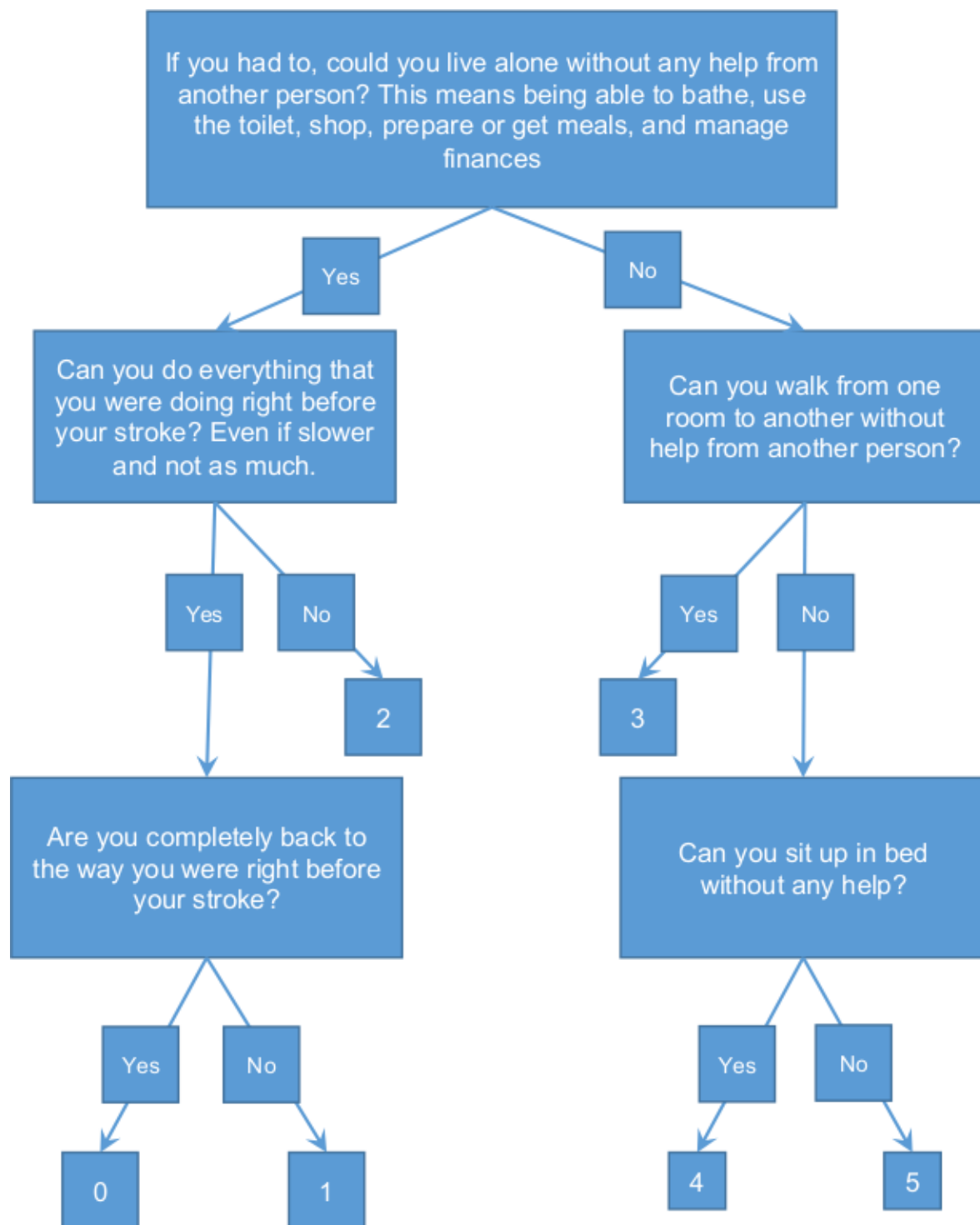
Supplementary Figure b. Small modified Ranking Scale questionnaire algorithm.

Secondary outcomes from questionnaire at 6 and 12 months

Before sending the 11-page questionnaire the Trial Manager Assistant (TMA) checked the patient's address and whether the patient was alive via a central registry.

The questionnaire included the smRSq questions illustrated in **Supplementary Figure b**, the Stroke Impact Scale (4–6), the EuroQoL (EQ5D-5L) (18) questions excluding the VAS-thermometer, the mental health inventory 5 (24,25) (MHI-5), as well as questions about how the patient lived – whether any carers came into their home – and what medications (if any) the patient was on.

The Stroke Impact Scale (SIS) (4–6) was used to provide an overall assessment of patient outcome as well as to allow us to assess the effect of treatment on specific outcomes of importance to the patients, the EuroQoL (EQ5D-5L) (18) to provide an overall measure of health-related quality of life. All scored out of 100 (best

possible QOL), the mental health inventory 5 (MHI-5) (24,25) to provide a measure of depression and anxiety, and the vitality subscale of SF Health Survey to assess patients' fatigue (26,27).

The letter ended with a question about who completed the questionnaire: the patient without help, the patients with some help, or completed by someone else.

Patients were encouraged to send back their questionnaire in a freepost envelope. The questionnaire was identical regarding instruments and questions at 6 and 12 months. For obvious reasons, there was a small difference in phrasing at the start and end.

In addition, we collected data on deaths, from all causes, through a central register.

Methods to increase retention at central 6 month follow up

All responses received were screened by the TMA, an experienced research nurse trained in the EFFECTS specific instrument. If there was missing data or inconsistent answers in questionnaires received, TMA called the patient (or next of kin) to complete the answers via the telephone.

Also, if we did not receive any answer at all in two weeks, the TMA telephoned the patient or next of kin, and the questionnaires were completed via telephone. Approximately 85% answered via mail directly without any reminder.

Secondary outcomes by face-to-face follow-up at 3 and 6 months. Local centre
- National Institutes of Health Stroke Scale (NIHSS) (6) to assess stroke severity as well as motor function and aphasia.
- Montreal Cognitive Assessment (MoCA) (13) to assess the patients' cognitive function.
- Physical Activity. The amount of exercise was graded according to the Saltin-Grimby Physical Activity Level Scale (SGPALS) (14,15).
- New diagnosis of depression since randomisation. (Definition, see below.)
- Adverse events. (Definition, see below.)
- Safety Outcomes (Definition, see below.)

Definition of new depression

In EFFECTS, we used four overlapping methods to capture a new depression:
1. At the 3- and 6-month local face-to-face follow-ups we assessed all patients according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (1) for major depression. If the DSM-IV criteria were fulfilled, we graded the depression using the Montgomery-Åsberg Depression Rating Scale (MADRS), and a total score of >19 confirmed the occurrence of a new depression (28).
2. At the 6-month central follow-up we asked all patients what medication they were prescribed. We coded all medication according to the Anatomical Therapeutic Chemical Classification (ATC) (29). If a patient was on an antidepressant – ATC-code beginning with N06A – the patient was defined as depressed. For further exploratory analysis, we grouped the antidepressant as follows:
    a. Non-selective monoamine reuptake inhibitors (N06AA04, N06AA09, N06AA10, N06AA21, N06AC).
    b. Selective serotonin reuptake inhibitors (N06AB03, N06AB04, N06AB05, N06AB06, N06AB08, N06AB10).
    c. Monoamine oxidase inhibitors (N06AF, N06AG02).
    d. Other antidepressants (N06AX03, N06AX11N06AX12, N06AX16, N06AX18, N06AX21, N06AX22, N06AX26).
3. If the depression was registered as an Adverse Event or Serious Adverse Event or if there was any attempt at suicide or self-harm it was considered as a depression.
4. Finally, if the study personnel had indicated depression as a reason for coming off study medication, we regarded this as a depression.

Definition of adverse events

All Adverse Events were reported by the local centres.

We did not have any patient diary. Patients and their carers were, however, given oral and written information of known side effects of fluoxetine and common problems after stroke.

Fluoxetine has been used since 1988 and its side effects are well known. Our aim was not to detect the plethora of symptoms and events that are common after stroke, and where the majority are probably not associated with either the stroke or fluoxetine. Instead, the purpose of our safety monitoring was to detect serious adverse events, e.g. Suspected Unexpected Serious Adverse Reactions or Serious Adverse Reactions (SAEs).

Initially, our centres reported large amounts of expected symptoms and events as adverse events, and our DMC urged us to find a system to differentiate the most important ones from the expected and commonplace. After writing a manual for SAE and discussing the issue at investigator meetings, the number of reports decreased substantially.

Confirmation of Adverse Events and Safety Outcomes

In EFFECTS, we did not have an event or outcome adjudication committee. Studies have showed that these do not significantly improve quality of data (30). Instead the adjudication of Adverse Events and Safety Outcome was done by the co-ordination centre (Chief Investigator, Trial Manager and Trial Manager Assistant). This was carried out prior to unblinding of the treatment code and we used rules to assure consistent assessment.

Definition of Safety Outcomes

We concentrated on the reporting of relevant adverse events found in the Cochrane 2012 review (31) that would affect safety, especially in stroke patients, and for those events we used the term Safety Outcomes.

The following safety outcomes were collected at the 3- and 6-month face-to-face follow-up by the local centre: new stroke (ischaemic or haemorrhagic), acute coronary events, upper gastrointestinal haemorrhage, new bone fractures, epileptic seizures, hyponatraemia (<130 mmol/L), and badly controlled diabetes.

Retrospectively, we also categorised patients with other serious bleeds (**Supplementary Table i**.) and thrombotic events (pulmonary embolism, arterial embolism) which lead to hospital admission. These were collected via the centres as SAEs.

Definitions of stroke

In EFFECTS, stroke was classified at randomisation by the local responsible physician. All patients had to undergo either a Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of the brain. A normal CT/MRI of the brain was compatible with an ischaemic stroke. If blood detected on the CT/MRI was likely to be due to haemorrhagic transformation, stroke was classified as ischemic. Hence, all strokes were categorised either as ischemic or intracerebral haemorrhage.

Further, the ischemic strokes were categorised using both the Oxfordshire Community Stroke Project (OCSP) (32) and modified TOAST (33) classification.

For OCSP, we used the algorithm described by Warlow *et al*, that consists of eight questions (34) which can be answered with *yes* (sign observed), *no* (sign not observed), or *0* (not assessable). The eight questions were:
- Unilateral weakness (and/or sensory deficit) affecting face?
- Unilateral weakness (and/or sensory deficit) affecting arm or hand?
- Unilateral weakness (and/or sensory deficit) affecting leg or foot?
- Dysphasia?
- Homonymous hemianopia?
- Visuospatial disorder (e.g. sensory or visual inattention, unable to copy pictures)?
- Brainstem or cerebellar signs (e.g. nystagmus or ataxia)
- Other neurological deficit?

Finally, the ischemic stroke was classified using the most likely cause, the modified TOAST criterion (33):
- Large artery disease, e.g. cortical stroke + carotid atheroma >50% with no other cause.
- Small vessel disease, e.g. lacunar stroke without carotid atheroma or cardiac source.
- Embolism from the heart, e.g. atrial fibrillation, prosthetic valve, endocarditis.
- Another cause, e.g. dissection, illicit drugs.
- Unknown or uncertain cause, no cause identified or more than one of above.

Definition of motor deficit and aphasia

We used parts of the NIHSS at randomisation to judge whether there was motor deficit or aphasia.

In EFFECTS, presence of motor deficit was defined as when the following criteria were met: One point or more on item 4 (Facial palsy) or, item 5 (Left or right arm motor drift) or, item 6 (Left or right leg motor drift).

Presence of aphasia was defined as one point or more on NIHSS item 9 (Language/aphasia).

Adherence and monitoring of adherence

Adherence to the trial medication was measured five times by the local team by asking the patient (or carer) how often the patient took the study medication. Questions and possible answers are given in **Supplementary Table c**).

Time	Question (Q) and answer alternative (AA)
Discharge	**Q**: Has patient started to take the study medication?
	AA: Yes/no; if yes, please note the date; if no, why?
1 week (telephone)	**Q**: How often did the patient take the study medication?
	AA: 7 days/week, 5-6 days/week, 3-4 days/week, 1-2 days/week, took some breaks in the study medication, stopped taking the study medication.
4 weeks (telephone)	Identical to 1 week
3 months (face-to-face)	Identical to 1 week
6 months (face-to face)	Identical to 1 week

Supplementary Table c. Adherence questions in EFFECTS. Adherence was defined as taking the study medication 7 days/week or 5-6 days/week, and intermediate adherence as taking the study medication 3-4 days/week, 1-2 days/week, or taking some breaks. When the patient had stopped taking the study medication, we noted the date and the reason. If the reason was an Adverse Event or Serious Adverse Advent, it was noted in the electronic CRF by the local study personnel.

Further, at 3 and 6 months we counted the remaining capsules. The external monitors from the Karolinska Trial Alliance randomly checked drug accountability for at least 10% of the patients and compared that with the notes in the charts and the dispensing log. We did not take a laboratory test for adherence.

If the responsible doctor suspected an adverse event, we recommend coming off the study medication for 14 days to see if the symptoms resolved. If the symptoms resolved, patients were recommended to restart to see if symptoms returned.

All breaks were registered in the eCRF. There was no limit to how long a temporary break might be. Adverse Events could be discussed with the co-ordinating centre during office hours. In addition, we had a 24/7 helpline for questions managed by the Chief Investigator.

Trial organisation

Co-ordination centre
The co-ordination centre was located at Karolinska Institutet, Department of Clinical Sciences Danderyd Hospital, and those responsible for day-to-day management were Chief Investigator Erik Lundström, Trial Manager Eva Isaksson and Trial Manager Assistant Nina Greilert.

Members of the Steering Committee
The Steering Committee consisted of Professor Katharina Stibrant Sunnerhagen (chair), Professor Per Wester, Professor Bo Norrving, Professor Håkan Wallén, Senior Professor Jörgen Borg, Senior Associate Professor Björn Mårtensson, Associate Professor/statistician Per Näsman, Chief Investigator/Associate Professor Erik Lundström, and Trial Manager Eva Isaksson. The co-chief investigators from FOCUS and AFFINITY were affiliated to the Steering Committee. We did not have any patient involvement in the steering committee nor when we wrote the protocol.

The Steering Committee was responsible for following the development of the study and assisting the Chief Investigator with advice and support when needed. Further, the Steering Committee ensured that a good publication policy was applied to the protocol which states that publications are prepared by persons approved by the Steering Committee.

The study is dependent on collaboration with a large number of doctors, nurses, patients and relatives. Those included in the local centre were included in a list (below).

EFFECTS Trial Collaboration
At each participating centre a Principal Investigator (PI) was responsible for identification, recruitment, data collection and completion of CRFs, along with the follow up of study patients and adherence to the study protocol and the investigators' brochure.

The PI were not part of the Steering Committee.

We have listed each centre with the total number of patients recruited, followed by the names of the local PIs, and other significant contributors *(patient recruitment and follow-up)* at that centre.

The centres are presented in order based on when they started. Also, we have given detailed information of centres and their recruitment in **Supplementary Table d**.

Danderyd Hospital (192): Ann Charlotte Laska (PI), Elisabeth Änggårdh Rooth, Anna Grünfeldt, Eva Isaksson, Nina Greilert Norin, Hillevi Asplund. Karolinska University Hospital Solna (126): Bjarni Gudmundsson (PI), Malin Säflund, Maria Axelsson, Malin Bodin, Anna-Maria Parlatore. Skaraborg Hospital Skövde (102): Björn Cederin (PI), Eric Bertholds, Eva Åkerhage, Max Fantenberg. Hässleholm Hospital (49): Magnus Esbjörnsson (PI), Krzysztof Grodon, Erika Snygg, Anna Zenthio, Theres Strandberg. Uppsala University Hospital (77): Bernice Wiberg (PI), Erik Lundström, Oskar Fasth, Signild Åsberg, Semira Duzo, Solveig Bergqvist-Persson, Eva-Lis Lundberg, Gladys Gahongore, Käthe Ström, Rose-Marie Brundin, Malin Edén. Karolinska University

Hospital Huddinge (15): Maria Lantz (PI), Ioanna Markaki, Caroline Bergmark, Gudrun Olsson-Skogman, Karin Söderquist, Kubra Talayhan, Magnus Hiis, Stefan Wrede. Mora Hospital (85): Jörg Teichert (PI), Solveig Östberg. Falu Hospital (22): Magnus Bergmann (PI), Mirja De Geer, Joakim Hambraeus, Monica Holst, Christina Nylen, Helen Luoma, Ingegerd Lönn, Sandra Johansson. Skaraborg Hospital Lidköping (12): Lennart Welin (PI), Anders Planck, Ingrid Roland, Sofia Wahll. Capio S:t Göran Hospital (77): Ulrika Löfmark (PI), Ahmad Ayad, Palpana Aikaterini, Christina Larsson, Gustaf Ahrenmark, Jan Mathé, Mezin Öthman, Marielle Anzén, Pirjo Perduv, Helena Thunberg. Visby Hospital (7): Sven-Erik Bysell (PI), Anna Vestberg-Bysell, Eva Smedberg. University Hospital of Umeå (15): Xiaolei Hu (PI), Per Wester, Britta Pettersson, Sara Korpela. Kristianstad Central Hospital (20): Axel Andersson (PI), Lena Eriksson. Norrtälje Hospital (9): Moa Gunnarsson (PI), Ann Engqvist, Hanna Hult, Annelie Fredlund, Linnea Nikander. Helsingborg Hospital (21): Pernilla Sandgren (PI), Camilla Werke, Petra Karlsson, Malin Karlsson. Skåne University Hospital Malmö (59): Eva Ask (PI), Martin Söderholm, Aniko Kuris, Elisabeth Poromaa, Natalie Montevert, Cecilia Johnsson. Halland Hospital Halmstad (74): Peter Thomasson-Sommer (PI), Miriam Morell-Larsen, Anders Funkquist, Lisbeth Andersson, Sofia Paulsson. Mälarsjukhuset Eskilstuna (36): Bo Danielsson (PI), Aleksander Saric, Anna-Karin Wärme, Christina Widhe-Qvist, Göran Pelang, Linnea Fransson, Åsa Byström, Malin Dalqvist. Rehab Station Stockholm (28): Liisa Hopia (PI), Sabahudin Bjelak, Ivan Sunara, Helen Lundberg, Rainer Gerdes, Leena Peltovuoma, Petra Engblom. Skåne University Hospital Lund (9): Andreas Arvidsson (PI), Irina Dragancea, Eva Engström, Lena Stankoska, Madeleine Rosen. Sundsvall Hospital (95): Fredrik Björck (PI), Vilhelm Sjögren, Anna Eelde, Anna Aronsson, Maria Kaldensjö. Sahlgrenska University Hospital (47): Anke Brederlau (PI), Arne Allardt, Anahita Nasouri, Annika Nordanstig, Cristina Gutierrez-Perez, Lukas Holmegaard, Maria Davidson, Mikael Jerndal, Margareta Ohlsson, Petra Redfors, Matilda Errind Arvgård, Stine Mathilde Hildal Fagerlind, Anna Bengtsson, Axel Hallingbäck, Anna Jacobson, Cecilia Damm, Lena Rosen. Högsbo Rehabilitation Hospital (2): Trandur Ulfarsson (PI), Marie Gustafsson. Stora Sköndal Neurologic Rehabilitation Clinic (16): Mehran Taklif (PI), Anna Sjöström, Ann-Kristina Hamrin, Åsa Samuelsson, Judith Treuter, Lena Lindvall. Östersund Hospital (95): Magnus Gibson (PI), Joachim Ögren, Linn Tander, Linda Wiklund. Alingsås Hospital (73): Brita Eklund (PI), Kjersti Hellqvist, Anna Lindh, Ida Abrahamsson, Karin Sjöström de Andrade, Maria Ekholm. Ängelholm Hospital (40): Björn Hedström (PI), Antonia Boldt-Christmas, Benny Ranebjer, Indre Valanciene, Annelie Rasmusson, Jenny Nilsson. Stockholm Sjukhem Neurologic Rehabilitation Center (29): Ellinore Richardsson, Jonas Björling, Helena Ekman, Pia Storbacka, Tarja Thiang. Örebro University Hospital (10): Daniel Merrick (PI), Anders Häggström, Lisa Ahlberg Jangentorp, Carina Ragnemyr. Northern Älvsborg County Hospital (7): Per Broman (PI), Ioanna Dagiasi, Marita Olofsson, Vivi-Anna Dahy. Stockholms Sjukhem Geriatrics (1): Max Mademyr-Larsson (PI), Anuja Withana, Carina Thoren, Haben Tekesteokbai. Västmanlands Hospital Västerås (42): Andreas Ranhem (PI), Ammar Yousif, Hannes Frejd, Per Lenngren, Catharina Holmberg, Joanna Nilsson Ryding, Linda Nyren, Maria Sellin, Sara Östring-Jalonen. Dalen Hospital (3): Camilla Ronnheden (PI), Dag Salej, Viktoria Westerlund, Ann-Christine Alvin, Catharina Ryberg, Helena Larsson, Maria Ljunggren. Lindesbergs Hospital (17): Martin Johansson (PI), Carl Bring, Kent Karlsson, Anna Wendelstam. Hudiksvalls Hospital (22): Anette Onkenhout (PI), Per-Gunnar Wiklund, Adam Lyren, Amanda Engberg, Moa Nordström, Sandra Åström, Viktoria Hjern.

Recruitment per centre

Centre	Principal Investigator	Type of centre	Stroke per year	Ready to include patient (yyyy-mm-dd)	First included patient (yyyy-mm-dd)	Days to first included patient	Total recruited patients	Percentage of recruited
Danderyd Hospital	Ann-Charlotte Laska	Specialised Non-university Hospital	895	2014-11-05	2014-11-11	6	192	13%
Karolinska University Hospital Solna	Bjarni Gudmundsson	University Hospital	369	2014-10-20	2014-10-20	0	126	8%
Skaraborg Hospital Skövde	Björn Cederin	Specialised Non-university Hospital	397	2015-03-01	2015-03-05	4	102	7%
Hässleholm Hospital	Magnus Esbjörnsson	Community Hospital	186	2015-03-16	2015-03-23	7	49	3%
Uppsala University Hospital	Bernice Wiberg	University Hospital	512	2015-03-20	2015-04-20	31	77	5%
Karolinska University Hospital Huddinge	Maria Lantz	University Hospital	383	2015-03-30	2015-04-08	9	15	1%
Mora Hospital	Jörg Teichert	Community Hospital	222	2015-04-08	2015-04-15	7	85	6%
Falu Hospital	Magnus Bergmann	Specialised Non-university Hospital	426	2015-05-04	2015-05-13	9	22	1%
Skaraborg Hospital Lidköping	Lennart Welin	Community Hospital	189	2015-06-18	2015-10-06	110	12	1%
Capio St. Göran Hospital	Ulrika Löfmark	Specialised Non-university Hospital	710	2015-06-18	2015-06-24	6	77	5%
Visby Hospital	Sven-Erik Bysell	Community Hospital	107	2015-07-13	2015-11-04	114	7	0%
University Hospital of Umeå	Xiaolei Hu	University Hospital	375	2015-08-10	2015-09-22	43	15	1%
Kristianstad Central Hospital	Axel Andersson	Specialised Non-university Hospital	350	2015-08-18	2015-09-24	37	20	1%
Norrtälje Hospital	Moa Gunnarsson	Community Hospital	171	2015-11-10	2015-12-09	29	9	1%
Helsingborg Hospital	Pernilla Sandgren	Specialised Non-university Hospital	417	2015-11-11	2015-11-18	7	21	1%
Skåne University Hospital Malmö	Eva Ask	University Hospital	600	2015-11-12	2015-12-18	36	59	4%
Halland Hospital Halmstad	Peter Thomasson-Sommer	Specialised Non-university Hospital	419	2015-11-13	2015-12-01	18	74	5%
Mälarsjukhuset Eskilstuna	Bo Danielsson	Specialised Non-university Hospital	274	2015-11-14	2015-22-23	9	36	2%
Rehab Station Stockholm	Liisa Hopia	Rehabilitation Medicine Hospital	NA	2015-11-15	2015-11-24	9	28	2%
Skåne University Hospital Lund	Andreas Arvidsson	University Hospital	598	2015-11-30	2016-02-29	91	9	1%
Sundsvall Hospital	Fredrik Björck	Specialised Non-university Hospital	406	2015-12-02	2015-12-18	16	95	6%
Sahlgrenska University Hospital	Anke Brederlau	University Hospital	677	2016-01-11	2015-04-15	95	47	3%

Centre	Principal Investigator	Type of centre	Stroke per year	Ready to include patient (yyyy-mm-dd)	First included patient (yyyy-mm-dd)	Days to first included patient	Total recruited patients	Percentage of recruited
Högsbo Rehabilitation Hospital	Trandur Ulfarsson	Rehabilitation Medicine Hospital	NA	2016-01-13	2016-03-04	51	2	0%
Stora Sköndal Neurologic Rehabilitation Clinic	Anna Sjöström	Rehabilitation Medicine Hospital	NA	2016-01-15	2016-01-22	7	16	1%
Östersund Hospital	Magnus Gibson	Specialised Non-university Hospital	332	2016-02-19	2016-03-10	20	61	4%
Alingsås Hospital	Brita Eklund	Community Hospital	197	2016-02-20	2016-02-25	5	73	5%
Ängelholm Hospital	Björn Hedström	Community Hospital	245	2016-02-21	2016-03-15	23	40	3%
Stockholm Sjukhem Neurologic Rehabilitation Centre	Ellinore Richardsson	Rehabilitation Medicine Hospital	NA	2016-02-22	2016-04-04	42	29	2%
Örebro University Hospital	Daniel Merrick	Rehabilitation Medicine Hospital	NA	2016-06-10	2016-10-10	122	10	1%
Northern Älvsborg County Hospital Trollhättan	Per Broman	Specialised Non-university Hospital	634	2016-10-05	2016-12-03	58	7	0%
Stockholm Sjukhem Geriatrics	Max Larsson	Geriatric Rehabilitation	NA	2016-10-13	2016-11-24	42	1	0%
Västmanland Hospital Västerås	Andreas Ranhem	Specialised Non-university Hospital	456	2016-12-05	2017-01-18	44	42	3%
Dalen Hospital	Camilla Ronnheden	Geriatric Rehabilitation	NA	2017-03-10	2017-05-22	73	3	0%
Lindesberg Hospital	Martin Johansson	Community Hospital	101	2017-03-10	2017-06-15	97	17	1%
Hudiksvall Hospital	Anette Onkenhout	Community Hospital	141	2017-04-05	2017-04-12	7	22	1%
TOTAL							1500	100%

Supplementary Table d illustrates all centres, principal investigators, type of centre, their numbers of strokes per year according to Riksstroke's annual report 2019 (35), when the centre was ready to include its first patient, date of first included patient, number of days to first included patient, total recruited and proportion of recruited patients in EFFECTS. NA=Not Applicable.

Monitoring of the study

Data Monitoring Committee
The Data Monitoring Committee (DMC) independently monitored patient safety and efficacy information during the trial.

The DMC comprised of two experienced stroke physicians: Senior Professor Kjell Asplund (chair), Senior Associate Professor Kerstin Hulter Åsberg, and a biostatistician, Anders Ljungström.

DMC members were not involved as Principal Investigators or sub-investigators in the study. Moreover, DMC members were not allowed to have a conflict of interest that would bias their review of trial data (e.g. financial interest that could be substantially affected by the outcome of the study, strong views on the relative merits of the study drug, relationships with individuals in trial leadership positions that could be considered reasonably likely to affect their objectivity, or involvement in any potentially competing trial).

The unblinded statistician – Anders Ljungström – prepared data and reports for the DMC to review. The Chief Investigator served as a primary contact person for the DMC and DMC issues.

Monitoring of EFFECTS
The majority of the monitoring was done centrally, however, online onsite monitoring and detailed source data verification by the Karolinska Trial Alliance was also done.

External monitoring by Karolinska Trial Alliance
Regular on-site monitoring visits were performed during the study depending on the enrolment rate according to a specific monitoring plan (36).

Data management and data cleaning
The task of data management, quality control and integrity were divided between the centres, the co-ordination centre at Karolinska Institutet, the Karolinska Trial Alliance and personnel from EDC Scandinavia AB.

We used OpenClinica® as our electronic Case Report Form (eCRF). Data entry in the eCRF was done at each centre. Almost all variables in our eCRF have had mandatory checks for inconsistent values (36).

Access to data
The final cleaned data set will be saved in Karolinska Institutet's electronic notebook (37). Trial statistician (PN) and Chief Investigator (EL) will have access to the data. All data will be stored anonymised, using the EFFECTS trial ID. A limited number of variables will be shared with the FOCUS and AFFINITY trial enabling the planned individual patient data meta-analysis.

The datasets used and/or analysed during the current study can be available from the corresponding author on reasonable request. However, according to the Swedish Secrecy Act 24:8, an interested researcher first must apply and receive approval from a Swedish Research Ethical Committee. Written proposals will be assessed by the EFFECTS Steering Committee and a decision made about the appropriateness of the use of data. A data sharing agreement will be put in place before any data are shared.

Ethics approval

The study was approved by the Research Ethical Committee (REC) in Stockholm, Sweden on 30th September 2013, number 2013/1265-31/2. All the 7 subsequent Amendments were approved by the same REC. Details of all Amendments and their justification are given in Supplementary Table k. Below follows date and number for all Amendments.

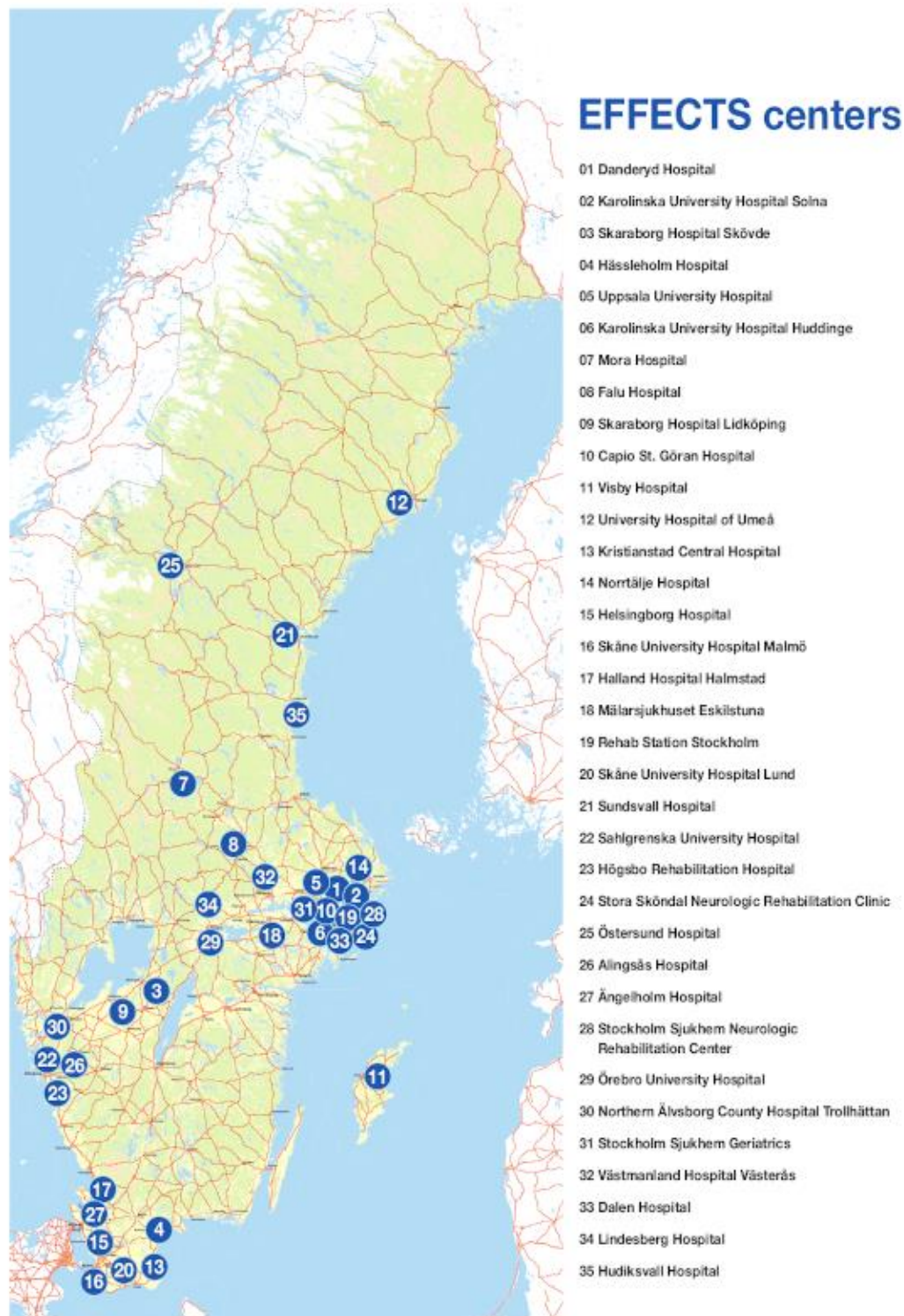- Amendment 1 (15th April 2015)
- Amendment 2 (Number: 2015/991-32. 10th June 2015)
- Amendment 3 (Number: 2015/2056-32. 30th November 2015)
- Amendment 4 (Number: 2016/1191-32. 14th June 2016)
- Amendment 5 (Number: 2016/2531-32. 4th January 2017)
- Amendment 6 (Number: 2017/638-32. 28th Mars 2017)
- Amendment 7 (Number: 2018/1012. 30th May 2018)

Funding and sponsor of the study

Supplemental Figure

EFFECTS centers

01 Danderyd Hospital

02 Karolinska University Hospital Solna

03 Skaraborg Hospital Skövde

04 Hässleholm Hospital

05 Uppsala University Hospital

06 Karolinska University Hospital Huddinge

07 Mora Hospital

08 Falu Hospital

09 Skaraborg Hospital Lidköping

10 Capio St. Göran Hospital

11 Visby Hospital

12 University Hospital of Umeå

13 Kristianstad Central Hospital

14 Norrtälje Hospital

15 Helsingborg Hospital

16 Skåne University Hospital Malmö

17 Halland Hospital Halmstad

18 Mälarsjukhuset Eskilstuna

19 Rehab Station Stockholm

20 Skåne University Hospital Lund

21 Sundsvall Hospital

22 Sahlgrenska University Hospital

23 Högsbo Rehabilitation Hospital

24 Stora Sköndal Neurologic Rehabilitation Clinic

25 Östersund Hospital

26 Alingsås Hospital

27 Ängelholm Hospital

28 Stockholm Sjukhem Neurologic Rehabilitation Center

29 Örebro University Hospital

30 Northern Älvsborg County Hospital Trollhättan

31 Stockholm Sjukhem Geriatrics

32 Västmanland Hospital Västerås

33 Dalen Hospital

34 Lindesberg Hospital

35 Hudiksvall Hospital

Supplementary Figure c. Every circle represents a centre in EFFECTS.

Supplemental Tables e–k

	Fluoxetine (n=750)		Placebo (n=750)		Riksstroke
	n	%	n	%	
Female sex	287	38%	288	38%	46%
Age, mean (SD), years	70·6 (11·3)		71·0 (10·5)		75
NIHSS at randomisation, median (IQR)	3·0 (2·0–6·0)		3·0 (2·0–6·0)		3
Living condition prior stroke					
Living with someone else	484	64%	467	62%	45%
Lives alone	266	36%	282	38%	47%
Assisted living	0		0		8%
Other	0		1	(0·13%)	
Independent before stroke	717	96%	728	97%	88%
Prior Medical history					
Coronary artery disease	123	16%	111	15%	NA
Ischaemic stroke/TIA	126	17%	131	18%	21% *
Diabetes	140	19%	159	21%	23%
Stroke diagnosis					
Non stroke	2	0·27%	1	0·13%	NA
Ischaemic stroke	661	88%	649	87%	86%
Intracerebral haemorrhage	87	12%	100	13%	13%
Revascularisation treatment					
Intravenous (IV) thrombolysis, n (%)	167	23%	158	22%	12.1%
Thrombectomy only, n (%)	10	1·4%	20	2·7%	0.5%
IV thrombolysis and thrombectomy, n (%)	177	24%	178	24%	16.8%

Supplementary Table e. Comparing EFFECTS with data from Riksstroke (38). * In Riksstroke data includes previous stroke only. NIHSS=National Institutes of Stroke Scale; TIA=Transient Ischaemic Attack; IV=Intravenous

Modified Rankin Scale	Description	Fluoxetine (n=737)		Placebo (n=742)	
		n	%	n	%
0	No symptoms.	156	21%	170	23%
1	No clinically significant disability despite symptoms.	216	29%	199	27%
2	Slight disability - unable to do everything.	94	13%	106	14%
3	Moderate disability - unable to live independently but can walk.	168	23%	164	22%
4	Moderately severe disability and unable to walk without help from another person.	46	6%	48	7%
5	Severe disability. Unable to sit up.	32	4%	33	4%
6	Dead.	25	3%	22	3%
Missing data		13	2%	8	1%

Supplementary Table f. Primary outcome of disability on the modified Rankin Scale at 6 months by treatment group. Ordinal analysis of the modified Rankin Scale (mRS) adjusted with logistic regression for the variables included in our minimisation algorithm. In total, we had mRS data available for 99% (1479/1500). For fluoxetine 98% (737/750), and 99% (742/750) in the placebo group.

	Group		Common Odds Ratio	95% CI		P-value
	Fluoxetine	Placebo		Lower	Upper	
Primary outcome	737	742	0·937	0·780	1·125	0·4558
Secondary outcomes						
Variables used in the minimisation						
Probability of being alive and independent at 6 months						
0 to ≤ 0·15	147	149	0·813	0·538	1·227	0·3243
0·16 to 1	603	601	0·984	0·803	1·206	0·8757
Delay from onset to randomisation						
2 to 8 days	566	570	0·974	0·791	1·199	0·8024
9 to 15 days	184	180	1·032	0·715	1·489	0·8659
Motor deficit						
No	237	217	0·851	0·608	1·190	0·3456
Yes	513	533	0·976	0·787	1·211	0·8260
Aphasia						
No	616	616	0·960	0·787	1·173	0·6916
Yes	134	134	1·017	0·663	1·559	0·9397
Other pre specified sub group analyses						
Stroke type						
Intracerebral	86	99	0·944	0·564	1·579	0·8250
Ischemic	662	650	0·973	0·802	1·181	0·7802
Age group						
≤ 70 years old	328	316	1·043	0·789	1·379	0·7663
> 70 years old	422	434	0·878	0·692	1·115	0·2855

Supplementary Table g. The primary outcome is adjusted for variables in the minimisation algorithm. All secondary outcomes were pre specified, and are un-adjusted.

Variables used in the minimization are: Probability of being alive and independent at 6 months using the Six Simple Variables model (5), delay from onset to randomization, motor deficit at inclusion, and aphasia at randomization.

Probability of being alive and independent at 6 months 0 to ≤ 0·15 indicates a more severe stroke (i.e. a lower probability of being alive and independent).

Other pre-specified sub group analyses were stroke type (intracerebral haemorrhage vs ischemic stroke) and age group (≤ 70 years vs > 70 years). There was no difference between fluoxetine and placebo in any of the prespecified groups.

	7 d/w		5-6 d/w		3–4 d/w		1–2 d/w		Some breaks		Stopped taking	
	Flu	Pla	Flu	Pla	Flu	Pla	Flu	Pla	Flu	Pla	Flu	Pla
1 week, n	703	693	2	4	0	0	0	1	10	22	15	15
4 weeks, n	658	682	0	2	1	0	0	0	19	18	43	34
3 months, n	630	622	3	3	1	0	0	0	25	42	63	60
6 months, n	594	595	4	3	0	0	0	0	0	0	68	75

Supplementary Table h. Adherence to fluoxetine and placebo for each follow-up are given in numbers. Flu=Fluoxetine; Pla=Placebo

Explanation	Fluoxetine	Placebo	Total
Unspecified haematuria	2	2	4
Haemorrhage of anus and rectum	2	1	3
Gastrointestinal haemorrhage, unspecified	2	0	2
Transluminal endoscopic reoperation for deep haemorrhage in urological surgery	0	1	1
Reoperation of deep bleeding, carotis	0	1	1
Retinal haemorrhage	0	1	1
Perforation of oesophagus	1	0	1
Total	7	6	13

Supplementary Table i. Data are n. Diagnosis included in "Other major bleeding".

Cause of Death	Fluoxetine	Placebo	Total
Ischemic stroke	10	5	15
Acute coronary events	5	8	13
Pneumonia	1	3	4
Intracerebral haemorrhage	2	0	2
Lung cancer	1	2	3
Pancreas cancer	0	1	1
Colon cancer	0	1	1
Malignant neoplasm of prostate	1	0	1
Subarachnoid haemorrhage, traumatic	1	0	1
Endocarditis	0	1	1
Sepsis	1	0	1
Chronic kidney disease	1	0	1
Subdural haematoma	1	0	1
Lung fibrosis	1	0	1
Unknown	0	1	1
Total	25	22	47

Supplementary table j. Data are n. Cause of death. Case fatality was low. Only 3·1% (47/1500) died within 6 months in EFFECTS.

Severity	Fluoxetine	Placebo	Total
Mild	148 (45·4%)	130 (39·4%)	278 (42·4%)
Medium	118 (36·2%)	130 (39·4%)	248 (37·8%)
Severe	60 (18·4%)	70 (21·2%)	130 (19·8)
Total	326 (100%)	330 (100%)	656 (100%)

Supplementary table k. Data are n (%). Adverse Events, reported by the local centre, graded in mild, medium and severe. Note that death in not included in this table.

Changes in protocol

Version	Revision	Justification
Version 4.2 Date 2013-06-28 **Version 4.3** Date 2013-09-17 Approval REC 2013-09-30 Approval MPA 2014-08-08	Version 4.2 was the original version when EFFECTS applied to the Research Ethical Committee (REC) and the Medical Product Agency (MPA). Version 4.3 after request from the REC and MPA.	We received some questions from REC regarding consent form (minor formulations) and made subsequent changes in the Patient Consent Form (v2) and from MPA regarding pharmaceutical documentation.
Version 4.4 Date 2015-01-05	No revision. Submitted to Medical Product Agency in Sweden	Co-chief Investigator Veronica Murray dies 2014-12-27
Version 4.5 Date 2015-03-15; Amendment 1 Approval 2015-04-15	Erik Lundström was appointed Chief Investigator and representant of the sponsor. Some changes in the Steering Committee. Clarifying of the health economic study.	The need for organisation changes. The health economic study was somewhat foggy.
Version 4.6 Date 2015-05-18; Amendment 2 Approval 2015-06-10	a) Changes in the patient consent form: The patient permits EFFECTS to obtain information from the central registry. We added "I also give my consent for information about being signed off sick, care-related consumption of resources and survival to be obtained from public registers. All data will be processed in anonymised form. Your personal data will be dealt with in accordance with the Swedish Data Protection Act. Danderyd Hospital is responsible for your personal data. You are entitled to receive an extract of your personal data once a year and can contact Eva Isaksson (tel. no. +46 (0)8 123 576 93) to obtain this." Some minor changes in the information about side effects in the consent. b) Page 19 first paragraph changes from "more than 7 000 observed" to "up to 6 100 observed patients" c) Page 21 paragraph 2.2.2. we added "Long-term data will also be retrieved from the Cause of Death Register and the National Patient Register, up to 3 years after inclusion of the last patient." d) Page 23, first paragraph, removal of the sentence "a printed eCRF, and a copy of all forms used." And we will add: "All forms will be possible to download from the trial website." e) Page 30-31. The sentence "The total amount of capsules for six months is 186 capsules of fluoxetine 20mg and 186 capsules of matching placebo;" will be changed "The total amount of capsules for six months is 200 capsules of fluoxetine 20mg and 200 capsules of matching placebo;" f) Page 35. Correction of the table: "10.1. STUDY ASSESSMENT SCHEDULE." We clarified the time interval. g) Page 36, last sentence "The patient and relatives will receive a diary in which they	a) We believe that registry date is a more appropriate and safer way to collect health economic data. At the same time, we do not need to burden the patients with questions. b) Should read 6 100 (not 7 000) d) We will not have any extra paper-CRF in the IB, The CRF can be downloaded via www.effects.se. e) For simplicity, we will give the patient 100 + 100 capsules of the study medication. f) Correction of table. g) We will not have any patient diary

Version	Revision	Justification
	are encouraged to record the date and nature of any adverse events." is removed	
	h) Page 36. Remove "… will be sent or faxed to the coordinating center ..." and "... If no discharge form is received by 6 weeks the center will be prompted by fax or email to send the discharge form. If the patient is still in hospital the local research team will be asked ..."	h) We want to simplify the process of the local center. To maintain security, we will encourage patient and relatives to call the local center to report. Our experience during the pilot phase is that this system works better, both patients and relatives find it easier to contact their local doctor or nurse.
	And the following sentence is also removed: "At these follow ups the GP or other responsible physician will be asked by the local EFFECTS-team about adverse events."	The writing that we will have a special system with pre-enveloped envelopes and a web-based solution for patient and relative will be deleted.
	Correction of the f/u: Face-to-face at 6 months, and central at 6 and 12 months. Removal of the possibility to have a web-based f/u.	We have reformulated the reading to match the follow-up performed (wrong writing in the protocol on this page), therefore we adjust the text to face-to-face follow-up at 6 months and supplementary central follow-up 6- and 12-months.
		We will not have any web-based follow-up available to patients and relatives.
	i) Page 37: Sample size correction, correction from 6000 to 6100.	i) Minor adjustments. since our sister trial AFFINITY will include 1 600 patients (not 1500), and the total sum in the pooled number will read 6100.
	The following incorrect text is removed: "The trial steering committee (TSC) will review the target sample size at the end of the feasibility phase and adjust this based on: • Advice from the DMC • Accruing data on • the enrolment into specific pre-specified subgroups • completeness of follow up • distribution of mRS categories in the population of enrolled subjects (i.e. both treatment groups combined), overall and in specific patient categories (e.g. those with motor deficits, aphasia, etc)	
	For example, if the distribution of mRS is different to that anticipated, then the sample size might need to be increased. This approach has the advantage that such sample size adjustments can be made without reference to the accumulating blinded data and avoids the need for conditional power calculations which can be unreliable."	
	j) Page 39. The following sentences will be removed: "In this case the total population will be 1550, if however, trial eligibility has had to be changed we will report the 1500 from the main phase as main findings, and the 50 from the feasibility phase separately."	j) We will recruit 1500 (not 1550) patients.
	Removal of the Fugl-Mayer scale and ANELT scale.	We will not use the Fugl-Mayer scale or ANELT (error writing).

Version	Revision	Justification
	k) Page 40. Adjustment of the number of EQ5D-5L measurements during the main phase; a decrease from the measurement during the pilot phase of EQ5D-5L at 6 occasions (1 week, 4 weeks, 3 months, 6 months and 12 months) to measure it at 3 measurement points (inclusion, 6 and 12 months).	k) We do not need 6 measurement points for quality of life.
	l) Page 43, Section 15.3.1, third paragraph. We sharpen the writing of SUSARs. It must be reported through the help-line within 24 hours instead of by fax. The sentence now reads "SUSAR should be reported to the Help-line (073- 663 74 44) within 24h."	l) Sharpening of the writing.
	m) Clarifying that the centers only need to have the latest version of the protocol in their investigator site file. Minor change in the CRF regarding MoCA. Removal of the Swedish personal security number.	
	n) Discharge form: Remove" Have there been changes in drug at baseline?"	n) Discharge form: The previous motivation was a bit unclear, to clarify and simplify reformulate.
	o) Changes in Patient Consent form v 2015-05-18 v3, clarification of possible side effects of fluoxetine, as well as the request to use registry data. The text now read: "I also agree that information on sick leave, health-related resource consumption and survival is obtained from public records. All data will be processed unidentified. Your personal information is handled in accordance with the Personal Data Act. Responsible for your personal information is Danderyd Hospital. You may retrieve your personal information once a year and contact Eva Isaksson (tel. 08 123 576 93)."	o) We believe that registry date is a more appropriate and safer way to collect health economic data. At the same time, we do not need to burden the patients with questions.
Version 4.7 Date 2015-11-12; Amendment 3 Approval 2015-11-30	Clarification of the health economic part of the trial, regarding EQ-5D and the use of VAS in the Stroke Impact Scale (SIS). We ensured that the VAS part of the EQ5D would be used in health economics.	
Amendment 4 Approval 2016-06-14	Clarification regarding the process of starting centers in EFFECTS. No protocol adjustments.	
Version 4.8 Date 2015-12-21; Amendment 5 Approval 2017-01-04	Page 24, exclusion criteria. The company that manufactures fluoxetine has updated its Summary of Product Characteristics. They now indicate that if metoprolol is used on indication heart failure, fluoxetine is contraindicated. EFFECTS Steering Committee and Safety Committee have concluded that this concerns serious heart failure that it may be clinically significant for more advanced heart failure (NYHA Grade III B – IV) and especially at higher doses and that co-administration of metoprolol and fluoxetine should be vigilant the interaction and early post-inclusion follow up the patient with clinical control including ECG. Addition to exclusion criteria	The company that manufactures fluoxetine has updated its Summary of Product Characteristics. We need to adopt to that.

Version	Revision	Justification
	"Fluoxetine is contra-indicated in combination with metoprolol used in cardiac failure New York Heart Association Grade III B and IV. At higher doses of metoprolol used on heart failure indication one should be vigilant of the interaction and early after enrollment monitor the patient with clinical monitoring including ECG."	
	Page 26. Co-enrolment Previously, we have written that participation in another CTIMP does not automatically exclude participation in EFFECTS, but it is important not to overload patients with studies. In the section on co-enrolment, we now refer to the TIMING study and add: "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."	Regarding co-enrollment, we specify in what extend we accept that.
	Page 29 Stopping Trial-treatment early. We have observed that our protocol has not specified how long we recommend stop IMP for suspected adverse reactions and whether we will allow re-insertion of medicines after a long period of time. In the updated version, we have now clarified. We now add: "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."	We specify stop for suspected adverse reactions and whether we will allow re-insertion of study medication.
	Page 52, Protocol Amendments In the protocol, we clarify that amendments relating to the addition of active centers in the study do not need to be sent to all centers as a protocol change. This is communicated in connection with major protocol changes as well as electronic via weekly newsletter and on the study's website (www.effects.se).	
Version 4.9 Date 2017-03-24; Amendment 6 Approval 2017-03-28	Change of Principal Investigator at centre 3, Skövde hospital and centre 6, Karolinska University Hospital Huddinge. Page 22. We will add: 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. (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 sends to the patients by the Trial Manager Assistant (TMA) at 6- and 12-month post randomisation. If the patient does not answer, the TMA contact the	Our primary outcome is the modified Rankin scale (mRS) measured with the small modified Rankins Scale (smRSq). The smRSq consists of five questions and can be conducted as survey or by telephone. smRSq is validated in English but not in Swedish. In our research plan, we have stated that we plan to do this in 2013. However, due to the fact that we have had to focus on other things (preparation of randomization systems, eCRF, inclusion of patients in the study), we have not completed the planned study. Since it has been several years since we applied, we consider it important to clarify

Version	Revision	Justification
	patient by phone and remind them to send in the questionnaire. If they have difficult to answer for themselves TMA helps them fill in the form by phone.	for the Regional Ethical Committee where we are in the matter. We intend to investigate whether the survey we send at 6 and 12 months - the small modified Rankins Scale (smRSq) - gives similar results to a traditional assessment as face-to-face modified Rankin Scale.
	Statistics <u>Number of patients</u> 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 enroll 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%.	
	<u>Statistical methods and data management</u> 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.	
Version 5.0 Date 2018-02-28; Amendment 7 Approval 2018-05-30	We changed PI for centre 2 Karolinska University Hospital Solna, centre 14 Norrtälje Hospital, centre 19 Rehab Station Stockholm, centre 24 Stora Sköndal Neurological rehabilitation	
	Permission for pooling 8 variables from Riksstroke registry regarding IV thrombolysis and thrombectomy:	
	1.Thrombolysis performed for stroke, 2. Date of thrombolysis therapy, 3. Thrombectomy or other catheter-based (endovascular) treatment for stroke, 4. Date of thrombectomy. 5. Need for assistance, 6. Mobility 7. Toilet visits, and 8. Dressing.	We believe it is important to know the proportion of patients receiving IV thrombolysis and thrombectomy. We want to compare the algorithm for smRSq and the variable used in Riksstroke registry. It is important to know what patients think is important for future research.

Version	Revision	Justification
	Permission to send priority questionnaire on future research to participants in EFFECTS.	
	We have added a version history of the protocol.	

Supplementary Table k. Protocol versions, revision history and their justifications.

Acknowledgements

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