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Update on the EFFECTS study of fluoxetine for stroke recovery: a randomised controlled trial in Sweden

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Abstract: Studies have suggested that fluoxetine might improve neurological recovery after stroke, but the results remain inconclusive. The EFFECTS (Efficacy oF Fluoxetine – a randomisEd Controlled Trial in Stroke) reached its recruitment target of 1500 patients in June 2019. The purpose of this article is to present all amendments to the protocol and describe how we formed the EFFECTS trial collaboration in Sweden.

Methods: In this investigator-led, multicentre, parallel-group, randomised, placebo-controlled trial, we enrolled non-depressed stroke patients aged 18 years or older between 2 and 15 days after stroke onset. The patients had a clinical diagnosis of stroke (ischaemic or intracerebral haemorrhage) with persisting focal neurological deficits. Patients were randomised to fluoxetine 20 mg or matching placebo capsules once daily for 6 months.

Results: Seven amendments were made and included clarification of drug interaction between fluoxetine and metoprolol and the use of metoprolol for severe heart failure as an exclusion criterion, inclusion of data from central Swedish registries and the Swedish Stroke Register, changes in informed consent from patients, and clarification of design of some sub-studies.
EFFECTS recruited 1500 patients at 35 centres in Sweden between 20 October 2014 and 28 June 2019. We plan to unblind the data in January 2020 and report the primary outcome in May 2020.

Conclusion: EFFECTS will provide data on the safety and efficacy of 6 months of treatment with fluoxetine after stroke in a Swedish health system setting. The data from EFFECTS will also contribute to an individual patient data meta-analysis.

Trial registration: EudraCT 2011-006130-16. Registered on 8 August 2014.
ISRCTN, ISRCTN13020412. Registered on 19 December 2014.
ClinicalTrials.gov: NCT02683213. Retrospectively registered on 2 February 2016.

Keywords: Stroke, Fluoxetine, Selective serotonin reuptake inhibitor, SSRI, Stroke recovery, Recovery of function, Multicentre study

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Introduction

Background

Globally, 13.7 million new strokes occur annually [1]. In Sweden, with a population of about 10 million inhabitants, about 23,000 people experience stroke annually [2]. Despite major improvements in the treatment of acute ischaemic stroke over the past 20 years, about half of all stroke survivors are left with long-term residual disability [3].

In 2011, the FLAME trial [4] reported promising results for the effects of fluoxetine on stroke recovery. FLAME was a randomised controlled trial (RCT) of 118 patients with ischaemic stroke and unilateral motor weakness; half of the patients were randomised to 20 mg fluoxetine and half to placebo daily for 3 months as well as receiving physiotherapy. At 3 months, the proportion of patients with a modified Rankin Scale (mRS) [5] of 0–2 was 17 absolute percent higher in the fluoxetine group (26% versus 9%, $p = 0.015$). A subsequent Cochrane review of 52 RCTs ($N = 4059$) of selective serotonin reuptake inhibitors (SSRIs) for stroke recovery [6] showed that SSRIs improved functional recovery after stroke. However, most trials were small and prone to systematic and random errors. The authors concluded that large, well-designed trials were needed to determine whether SSRIs were indeed safe and effective in improving functional outcome after stroke.

This led us to develop a family of three large trials of fluoxetine for stroke recovery [7]: EFFECTS (Efficacy oF Fluoxetine – a randomisEd Controlled Trial in Stroke), AFFINITY (The Assessment oF FluoxetINe In sTroke recovery) and FOCUS (Fluoxetine Or Control Under Supervision) [8]. Each trial was funded and run separately with oversight from its own Steering Committee. We hypothesised that the routine administration of 20 mg fluoxetine once daily in the 6 months after an acute stroke improves the patient's functional outcome.

The FOCUS trial ($N = 3127$) is the only trial to date to have finished and published its results [8]. For the primary outcome measure, the distribution across mRS categories at 6 months was similar in the fluoxetine and placebo groups (common odds ratio adjusted for minimisation variables 0.95 [95% CI 0.84–1.08]; $p = 0.44$). Patients allocated fluoxetine were less likely than those allocated placebo to develop new depression by 6 months (13.4% vs 17.2%, $p = 0.0033$), but they had more bone fractures (2.9% vs 1.5%; $p = 0.007$).

The EFFECTS ($N = 1500$) and AFFINITY ($N = 1280$) trials finished their recruitment in June 2019 and are due to report their primary outcome at the stroke conference jointly organised by the European Stroke Organisation and the World Stroke Organization in Vienna in May 2020. Further, we plan to present an individual patient data meta-analysis from the three trials. Finally, we will combine our data and update the Cochrane systematic review of selective serotonin reuptake inhibitors (SSRIs) for stroke recovery [6].

This update follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist [9] in combination with the 2013 SPIRIT explanation and elaboration guidance for protocols of clinical trials [10] (Additional files 1 and 2).

The purpose of this update is to present all amendments to EFFECTS and describe how we formed the EFFECTS trial collaboration. We also describe the settings and locations in which the study was performed.

Methods

Design overview

EFFECTS is a multicentre, randomised, placebo-controlled, blinded, parallel group trial of fluoxetine for stroke recovery performed at 35 centres in Sweden. Primary outcome was the mRS at 6 months. Recruitment started 20 October 2014 and ended 28 June 2019, when the target of 1500 patients was met. We plan to unblind the dataset when the last patient has had their 6-month follow-up in January 2020 and report the primary outcome in May 2020.

For description of the core study protocol, including study procedures and data collection, allocation and blinding procedures, we refer to the published trial protocol publication [7] and statistical analysis plan [11].

Important changes after trial commencement

During the course of the study, we made seven amendments to the protocol. All these amendments, the Research Ethical Committee approvals and the approvals from the Swedish Medical Product Agency are available in Additional file 3. For convenience, we have summarised the amendments and their justification in a table (Additional file 4).

The latest version of the protocol (version 5.0 28 February 2018) is available online on the study's website [12]. All previous versions including amendments were published on the homepage and communicated to active centres during the course of the study.

Below, we list the two most important changes.

1. In Amendment 2, we changed the patient consent form. In this version, the patient permits EFFECTS to obtain information from the central Swedish registries regarding sick leave, care-related consumption of resources and survival. Registry data are more accurate when collecting health economics data than asking patients for this information [13]. In this way, the responder burden for patients was reduced.
   Amendment 2 was approved 10 June 2015. All patients who had signed the old consent form (25

April 2013, v 2), had to re-sign the new version (18 May 2015, v 3). On 25 May 2018, the General Data Protection Regulation (GDPR) was implemented. Since GDPR is a regulation governed by EU law, we had to change the consent form, which is reflected in v 4, 25 May 2018 (Additional file 5). This change, however, was not accompanied by any amendment or re-signing of consent. We informed all patients who had signed the previous consents via a personal letter and updated our homepage with the information.

2. About safety. The company that manufactured our Investigational Medicinal Product, informed us on 22 November 2016 that they had updated their Summary of Product Characteristics. EFFECTS Steering Committee and Data Monitoring Committee concluded that a serious interaction between metoprolol and fluoxetine may be clinically significant for more advanced heart failure. Consequently, we added the following exclusion criteria:
"Fluoxetine is contra-indicated in combination with metoprolol used in cardiac failure New York Heart Association Grade III B–IV."
Further, we clarified that patients treated with higher doses of metoprolol (> 100 mg/day) on the indication of heart failure, early after enrolment, should be monitored clinically and with an electrocardiogram.
For safety reasons, we carried out a review of the medical charts of patients currently on metoprolol. Our Data Management Committee did not find any indication of serious interaction after reviewing the unblinded data and advised the Chief Investigator and the Steering Committee to carry on.
Amendment 5. Approval 4 January 2017.

Settings and locations where the data were collected

EFFECTS is performed in Sweden in which the health care is tax funded and fairly equally distributed throughout the country [14]. The government establish principles and guidelines, and sets the political agenda for health and medical care. Sweden is divided into 20 regions, each responsible for the health care in its particular area. In Sweden, hospitals can be divided in three types: university hospitals, specialised non-university hospitals, and community hospitals [15]. There is acute stroke care in all these, in total, 72 hospitals.

Stroke in Sweden data from Riksstroke 2018

In 2018, there were 21,124 strokes registered in Riksstroke – the Swedish stroke registry [2]. With a coverage of 90% of all strokes the estimated number of strokes is 23,735.

Ischaemic stroke accounts for 86% and intracerebral haemorrhage for 14%. In 2018, 63% had mild strokes, defined as National Institutes of Health Stroke Scale (NIHSS) 0–5 points. The mean NIHSS was 6 and the median 3 points.

More men (54%) than women (46%) have a stroke. The mean age is 75 years, 73 for men and 78 for women. Sixty-four per cent of the stroke patients have high blood pressure, 29% atrial fibrillation, 23% diabetes and 14% are smokers at onset.

Standard care of stroke in Sweden

In 2018, 17% of all patients with ischaemic stroke were treated with reperfusion therapy; 14% with intravenous thrombolysis only, or intravenous thrombolysis in combination with thrombectomy. Reperfusion treatment has almost tripled since 2010.

The proportion of acute stroke patients treated at a stroke unit at some point during their hospital stay is high – 92%. The median length of stay in hospital is 7 days, with substantial variation between the hospitals. One reason for the variation could be different application of early supported discharge. Approximately 85% of patients are evaluated by a physical or occupational therapist, and around a third of the patients had their speech and swallow function evaluated by a speech therapist during the hospital stay.

Three out of four return to their own home after discharge. Of those one in four are judged to have no need of any rehabilitation, according to staff at the discharging hospital.

In EFFECTS, we did not give any specific instructions to health-care personnel regarding physical or other types of training, although the local centre registered, organised and individualised training for each patient. Patients received stroke rehabilitation according to their local stroke team's routines during the treatment period.

Results

Building a network, training the study personnel and initiation of sites

Early in the process we decided to meet potential investigators at their hospitals face to face instead of relying on email or telephone. This decision was based on intuition rather than a review of the literature and it led to more than 100 travelling days for the chief investigator and the trial manager.

How we reached out to a potential centre

First, we reached out to people we have previously worked with in the International Stroke Trial 3 [16]. This was done by a brief email about the rationale behind EFFECTS, an estimate of the time commitment, and the financial compensation for participation in the study. If the centre was interested in joining the trial, the principal

investigator (PI) at each centre sent in an Expression of Interest/Eligibility form and we scheduled a Site Initiation Visit (SIV) as soon as possible. The SIV was described as an information meeting and was carried out during lunchtime. All staff at the stroke unit, and where appropriate, outpatient service, were welcomed to participate in the SIV, but it was mandatory for the intended PI and the trial nurse. For the PI and trial nurse, the meeting could last from 1 to 3 hours, depending on how familiar the centre was with RCT participation.

Second, we used the Riksstroke report to identify Stroke Units with medium to high volume care. If a centre had been awarded *Stroke Unit of the Year*, or received an *Excellent Stroke Care* mention in Riksstroke, we contacted the centre, regardless of its size.

Third, we attended several stroke meetings in Sweden and one Nordic Stroke Meeting (held in Malmö, Sweden) with an EFFECTS exhibition (Table 1).

Finally, on two occasions, we carried out feasibility studies in which we examined whether eligible patients and interested study personnel were available.

The study personnel were not given any personal monetary compensation. The centre, however, received 5000 SEK for each included patient. There was no upper limit to how many patients the centre could include. The EFFECTS study was done in parallel with the usual health care in Sweden.

All patients were covered by the Swedish medical insurance [17].

Site initiation visit

All personnel – during a working lunch meeting (1 hour) The following items were discussed with the sites:

- The rationale, scientific background and hypothesis. (Chief investigator, approximately 20 minutes)

Table 1 Estimated time/patient required for the local centre

Item	Time
Screening	5 min
Inclusion	60 min
1 week telephone follow-up	5 min
1 month telephone follow-up	5 min
3 months follow-up (face-to-face; sometimes by telephone)	30 min
6 months follow-up, face-to-face	60 min
7 months telephone follow-up	30 min
Entering data into the electronic case report system	60 min
Answering queries	60 min

Other: We arranged training for the study personnel in study specific moments (4 h) and Good Clinical Practice (4 h). In addition, we organised 4 investigator meetings in Sweden (1 day per meeting) and 5 meetings at European Stroke Conferences.

- Inclusion and exclusion criteria. Follow-up. Brief introduction to randomisation and follow-up. (Trial manager, approximately 20 minutes)
- Questions and answers (All, 20 minutes)

PI and trial nurse(s) – extended meeting after the lunch (1–3 hours) After the lunch, the trial manager and the chief investigator discussed the following in detail:

- Study protocol
- Procedure for informed consent
- Patient recruitment plan/screening activities/ enrolment
- Facilities and study personnel
- Randomisation procedure
- Investigational Medicinal Product handling and accountability
- Essential documents
- How the Case Report Form is filled out
- Safety reporting (adverse events/serious adverse events) and procedures for collection and documentation
- Good Clinical Practice (GCP) training and curriculum vitae

Finally, the Investigator Study File was handed over and discussed. The Investigator Study File contained essential documents required according to GCP. After all essential documents were signed and sent to the coordinating centre the study personnel (listed in the delegation log) were given access to the randomisations system and the centre was approved as active, ready to recruit patients.

Time for the local centre

Table 1 illustrates the time commitment for a typical patient and their follow-ups at the local centre.

Organisation and training of an EFFECTS centre

At each centre, we established a delegation list and persons on that list are referred to as study personnel. The study personnel consisted of a minimum of two people: one principal investigator (an experienced stroke physician) and one responsible trial nurse (registered nurse), both trained in GCP, the trial-specific procedures and our electronic Case Report Form (eCRF).

Further co-investigators (physicians) or trial nurses (registered nurses) were added at the discretion of the local principal investigator. We had no upper limit on how many study personnel were allowed on the delegation list, but all people who performed study-specific tasks had to be trained in GCP, study-specific instruments and eCRF. The training was organised by the co-

ordinating centre at Karolinska Institutet, either at the local site or at special central training days. In total, we trained over 150 study personnel in EFFECTS. A list of all centres and study personnel is available as Additional file 6.

EFFECTS recruited patients from acute stroke and rehabilitation units. Around 3% of Swedish stroke patients go to a rehabilitation unit.

The reason for recruiting from rehabilitation units was that the median length of stay in hospital in Sweden is short – especially in the Stockholm region – and since it was possible to include patients until 15 days post stroke, we thought it would be possible to include individuals at rehabilitations units.

Discussion

EFFECTS proves that it is possible to carry out a large investigator-led RCT in a country with only 10 million inhabitants. In fact, EFFECTS is now the largest ever stroke RCT conducted in Sweden. Further, EFFECTS is the second largest RCT of fluoxetine for stroke recovery after the FOCUS trial [8].

As a family of three investigator-led RCTs, EFFECTS, AFFINITY and FOCUS provide several benefits. Together, we wrote a strong core protocol and applied for funding in our respective countries and tailored study methods to each national setting(s). EFFECTS was able to use the same randomisation system and purchase the study drug from the same provider as FOCUS, which saved months of work. However, most important of all was probably the transfer of knowledge from experienced trialist to less experienced.

Although EFFECTS succeeded in reaching its target of 1500 participants, one major limitation was that it took longer than anticipated. We believe that the lack of a stroke research network was the main culprit. While we were able to build on an old informal network from the International Stroke Trial 3 (IST-3) [18], in many cases the previous PI or trial nurse had retired or moved. Basically, we had to build up and train our own stroke research network from scratch. In the United Kingdom, where there is a centrally funded network to support trials, our sister study FOCUS proved that recruitment rates were faster.

Data from EFFECTS will test the external validity of the FOCUS trial results and increase the precision of the estimates of the efficacy and safety of fluoxetine in ischaemic and haemorrhagic stroke. The planned individual patient data meta-analysis of EFFECTS, AFFINITY and FOCUS [8], as well as a subsequent update of the Cochrane systematic review [6] will likely give us a definitive answer as to whether fluoxetine has any role to play in stroke recovery.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-020-4124-7.

Additional file 1. SPIRIT 2013 Checklist for EFFECTS.

Additional file 2. WHO Trial Registration Data Set for the EFFECTS trial.

Additional file 3. Research Ethical Committee and the Swedish Medical Product Agency approvals for EFFECTS.

Additional file 4. Overview of protocol versions in EFFECTS.

Additional file 5. Consent to participate in EFFECTS and consent regarding handling notes and data management.

Additional file 6. List of centre and study personnel in EFFECTS.

Additional file 7. Monitoring Plan.

Additional file 8. Data Management Plan for EFFECTS.

Additional file 9. Data Review Plan (DRP) for EFFECTS.

Additional file 10. EFFECTS latest DMC charter.

Abbreviations

AFFINITY: The Assessment oF FluoxetINe In sTroke recoverY (AFFINITY); DMC: Data Monitoring Committee; eCRF: Electronic Case Report Form; EFFECTS: Efficacy oF Fluoxetine – a randomisEd Controlled Trial in Stroke; FOCUS: Fluoxetine Or Control Under Supervision; GCP: Good Clinical Practice; GDPR: General Data Protection Regulation; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; PI: Principal investigator; RCT: Randomised controlled trial; SIV: Site Initiation Visit; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; SSRI: Selective serotonin reuptake inhibitor

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Management

Co-ordination centre

The co-ordination centre was located at Karolinska Institutet Department of Clinical Sciences Danderyd Hospital, and those responsible for the day-to-day management were chief investigator Erik Lundström, trial manager Eva Isaksson and trial manager assistant Nina Greilert.

Steering Committee's responsibilities

The Steering Committee is responsible for following the development of the study, assisting the chief investigator with advice and support when required.

The Steering Committee is also responsible for:

1. Ensuring that the protocol for the study is followed.
2. Policies, superior organisational issues and any technical issues.
3. Analysing the reports from the Data Management Committee.
4. Monitoring finances in collaboration with Karolinska Institutet, which is the financial manager and manages the funds.
5. Overseeing staff; however, Karolinska Institutet has the responsibility for personnel.
6. Considering the need for any protocol changes.
7. If any sub-studies are planned within the framework of the main study, they should be presented orally first, on condition that the Steering Committee considers the study to be feasible and scientifically sound, and that it does not affect the main study. A written project report has to be submitted and approved by the Steering Committee before any application is sent. A signed (by the chair of the Steering Committee after approval by the Steering Committee) project plan should be filed at Karolinska Institutet. When submitting an application for ethics approval or funds, the chair of the Steering Committee and the chief investigator should be informed of this before submission. No changes may be made to an approved protocol without this being approved and signed in accordance with the conditions presented above.

Members of the Steering Committee

The Steering Committee consists 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 have not had any patient involvement in the Steering Committee nor when we wrote the protocol.

Monitoring of EFFECTS

Most of the monitoring was carried out centrally, however, online onsite monitoring and detailed source data verification by Karolinska Trial Alliance was also carried out (Additional file 7).

External monitoring by Karolinska Trial Alliance

Regular onsite monitoring visits were performed during the study depending on the enrolment rate and according to a specific monitoring plan.

Monitoring was performed according to ICH-GCP, Declaration of Helsinki, CRO SOPs for monitoring and the monitoring plan.

The first routine study monitoring visit was performed at each site when a few patients were randomised into the study, to confirm informed consent procedure, subject eligibility, ensure that the site was familiar with study drug management, detect possible problems and provide advice on how to complete the eCRF.

Source data verification was performed according to the monitoring plan throughout the study. The monitor ensured that 100% of all patients had signed the informed consent and verified that essential documents were available and up to date in the Investigator Study File continuously during the study. In addition, the external monitors carried out a 10% source data verification and drug accountability.

After each monitoring visit, the monitor sent a report to the sites and a copy of the report to the co-ordinating centre at Karolinska Institutet, and the representative for the sponsor. The report included a summary of the monitoring and highlighted issues that need to be followed up by the sites.

Close-out visit:

When the last patient has completed the study or when a site has been closed in advance, the monitor carried out a close-out visit at each site. At this visit the following were discussed:

- Possible remaining unsolved eCRF queries
- Investigator Study File completeness
- Possible remaining unresolved issues
- Patients: screened, randomised and complete
- Study drug accountability log completed
- Safety reporting (adverse events/serious adverse events)
- Information to study team regarding study report and archiving

Study drugs returned by the patients and remaining study drugs at the sites were sent for destruction to Apoteket AB, Sweden.

Dissemination policy

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 (who were on the delegation list) were included in a list (Additional file 6). The publication was prepared by a writing committee following the current International Committee of Medical Journals Editors Recommendations [19].

Data management and data cleaning

The task of data management, quality and integrity was shared by the centres, co-ordination centre at Karolinska Institutet, Karolinska Trial Alliance and personnel from EDC Scandinavia AB (Additional files 8 and 9).

We used OpenClinica® as our eCRF. Data entries in the eCRF were done at each at centre. Almost all variables in our eCRF have mandatory checks for inconsistent values.

In addition, there is an audit trail and the possibility to send queries within the system.

The data cleaning process was carried out by the co-ordination centre at Karolinska Institutet and began when the first 500 patients had finalised their 12-month follow-up. The process was ongoing until the last patient was followed up.

All central follow-ups at 6 and 12 months were mailed out from the co-ordination centre. If the study subjects did not return their questionnaire, we reminded the patient by telephone; then the patient either returned the questionnaire or more often the patient gave their answers over the telephone.

All follow-up forms were processed by a research assistant, and another research assistant cross-checked 100% of the primary outcome (smRSq) and 10% of data.

Confidentiality

All study-related information was stored securely at the local centre in locked filing cabinets in areas with limited access. All reports, data collection, processes and administrative forms are identified by an EFFECTS trial ID number to maintain patients' confidentiality. All records that contain names or other personal identifiers, such as informed consent forms, are stored separately from study records identified by code number. The central database is located at a secure server with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information are stored in a separate, locked file in an area with limited access as well as in Karolinska Institutet's electronic notebook [20].

Access to data

The final cleaned data set will be saved in Karolinska Institutet's electronic notebook [20]. Trial statistician (PN) and chief investigator (EL) will have access to the data. A limited number of variables will be shared with the FOCUS and AFFINITY trials enabling the planned individual patient data (IPD) meta-analysis. All data will be stored anonymised, using the EFFECTS trial ID.

Details of assessment and collection as well as processes to promote data quality can be found in the (Additional files 8 and 9).

Data collection forms (in Swedish) can be found on our homepage, www.effects.se.

In summary, the responsibilities were divided up as follows:

Database design	EDC Scandinavia
eCRF design	EDC Scandinavia, Co-ordination Centre at Karolinska Institutet and Karolinska Trial Alliance
Server management	EDC Scandinavia
Data collection	Centre and Co-ordination Centre at Karolinska Institutet

(Continued)

Data manager	EDC Scandinavia
CRF annotation	Centre, Co-ordination Centre at Karolinska Institutet and Karolinska Trial Alliance
Data entry	Centre, Co-ordination Centre at Karolinska Institutet and Karolinska Trial Alliance
Monitoring	Karolinska Trial Alliance
Source data verifications	Karolinska Trial Alliance
Issue and resolve data correction forms	Co-ordination Centre at Karolinska Institutet and Karolinska Trial Alliance
Medical coding	Co-ordination Centre at Karolinska Institutet
Data validation	EDC Scandinavia and Co-ordination Centre at Karolinska Institutet
Discrepancy management	Centre, Co-ordination Centre at Karolinska Institutet and Karolinska Trial Alliance
Database lock. The database will be preserved according to Karolinska Institutet's rules, the electronic notebook [20].	EDC Scandinavia

Data Monitoring Committee

The Data Monitoring Committee (DMC) independently monitored patient safety and efficacy information during the trial (Additional file 10). 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. In addition, DMC members were not allowed to have a conflict of interest that would bias their review of trial data (e.g. financial interests 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 potential 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.

Review meetings for the DMC

The DMC chairman ensured that DMC contacts and consultants were not inappropriately exposed to unblinded data made available to the DMC.

The DMC was an independent expert advisory group commissioned and charged with the responsibility for evaluating cumulative safety, efficacy and other clinical trial data at regular intervals. As such, the primary objective of the DMC was to monitor the safety of the subjects in the study by reviewing the available clinical data at scheduled time points including at least yearly meetings (which may be face to face or via teleconference) and on an ad hoc basis as required.

After the review of each data report was completed, the DMC chair provided the official DMC recommendation to the sponsor, the chief investigator and the chair of the Steering Committee regarding the appropriateness of continuing the study, from a safety and efficacy perspective, as well as any other recommendations relevant to study conduct and/or patient safety.

Specifically, the DMC members were authorised and expected to perform the following functions:

- Safeguard the interests of trial participants.
- Provide approval for and operate in accordance with the specifications outlined in the DMC Charter.
- Monitor the safety and efficacy of the trial intervention, through scheduled review of accumulating clinical data from the EFFECTS study and taking into account information from external sources.
- Consider the need for additional unscheduled reviews of study data.
- Review and evaluate the content of all unblinded data reports received.
- Ensure the confidentiality of all information received relating to the trial.
- In the event of further funding being required, to provide the Steering Committee and funder(s) with appropriate information and advice on the data gathered to date in a manner that will as far as possible protect the integrity of the study.
- Participate in and vote on DMC recommendations, bearing in mind the fact that ethical considerations are of prime importance.
- Make clear recommendations to the Steering Committee, with the Steering Committee chair as the principal contact.
- The DMC reviewed safety outcomes, including serious adverse events. Review of safety data occurred after 150, 300, 600, 900 and 1200 patients' 6-month follow-up data. No formal boundaries were used for terminating the study for safety reasons, but clear and consistent evidence of net harm that overrides any benefit should be apparent.
- A formal interim analysis to assess efficacy was done when approximately 67% of the planned primary efficacy events had accrued. The DMC was able to recommend early termination of the trial for the overwhelming superiority of fluoxetine over control. A modified Haybittle-Peto monitoring boundary was used as a guideline. If the primary efficacy comparison exceeds four standard errors in value, the DMC will initiate another interim analysis to be performed a minimum of 3 months later. If the monitoring boundary remains crossed, the DMC may recommend that the trial for the overwhelming superior efficacy of fluoxetine be terminated early. No adjustment of the significance level for the final analysis is required.

The DMC did not make any recommendations on whether the trial should be stopped on the basis of futility, i.e. that the trial – if it recruits to its target sample size – is unlikely to demonstrate a benefit from the trial of fluoxetine.

Throughout the trial, the DMC chair took responsibility for the committee's operations and authorised and assigned the following responsibilities:

- Chair DMC data review meetings.
- Ensured that all relevant data have been reviewed by the DMC members and that all issues have been addressed.
- Ensured that blinded individuals (i.e. the DMC coordinator, DMC contacts, and DMC consultants) were not inappropriately exposed to confidential and/or unblinded data.
- Ensured that only the members of the DMC were present during DMC deliberations, when DMC recommendations were discussed, and DMC voting procedures were conducted.
- Ensured the generation of confidential, written minutes of all closed sessions of any DMC meetings and maintained these minutes as confidential to DMC members only, until the final (end of study) database lock was completed.
- Ensured DMC approval of minutes of open and final sessions of all DMC meetings.
- Communicated, authored, signed, and provided the official, final recommendations of the DMC within specified timelines and according to the specifications outlined in the charter. If the DMC was divided in opinion on any major issue affecting the DMC's recommendation to the sponsor and EFFECTS Steering Committee, the DMC chair was responsible for assembling and presenting the majority and dissenting opinions for all recommendations considered.
- Arranged for consultation(s) and/or request additional data, as deemed necessary.
- If deemed appropriate by the DMC, at appropriate intervals, arrange a teleconference meeting with the chairs of the DMC committees for the FOCUS (Professor Peter Langhorne) and AFFINITY (Professor Robert Herbert, Australia) trials. If necessary, to discuss accumulating data in strict confidence and any implications for the continuation of each of the trials. Each chair may then subsequently need to consider whether to arrange a meeting of their respective trial DCM to discuss any issues that may arise from this liaison group.
- Maintain a secure central file of all data outputs received for DMC review and all minutes of all sessions of DMC meetings. Provide the sponsor with a copy of this file, through the chief investigator, once the final (end of study) database lock is complete.

Principal Investigator at each centre

At each participating centre, a PI is responsible for identification, recruitment, data collection and completion of CRFs, along with follow-up of study patients and adherence to the study protocol and the investigators' brochure. The PI is not part of the Steering Committee.

Authors' contributions

Associate Professor Erik Lundström (Neurologist, Uppsala University and Karolinska Institutet, 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 the first draft of the manuscript. Research Nurse Eva Isaksson (PhD student, Karolinska Institutet, Sweden) was the trial manager, participated in the Steering Committee, was involved in the design of the trial, and collected, verified, analysed data, and contributed to the first draft of the manuscript. Associate Professor Per Näsman (Statistician, KTH Royal Institute of Technology, Sweden) participated in the Steering Committee, was involved in the design of the trial, wrote the first draft of the statistical analysis plan, verified, and analysed data. Associate Professor Björn Mårtensson (Psychiatrist, Karolinska Institutet, Sweden) participated in the Steering Committee, advised on the management of depression within the trial and was involved in the design of the trial. Professor Katharina Stibrant Sunnerhagen (Rehabilitation Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden) was chair of the Steering Committee, and was involved in the design of the trial. Professor Per Wester (Stroke Physician, Umeå University and Karolinska Institutet, Sweden), Professor Håkan Wallén (Cardiologist, Karolinska Institutet, Sweden), Senior Professor Jörgen Borg (Rehabilitation Medicine, Karolinska Institutet, Sweden) participated in the Steering Committee and were involved in the design of the trial. 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 (Epidemiologist, University of New South Wales, Australia) were involved in the trial design, were affiliated with the Steering Committee and analysed data. All members of the writing committee have refined the study protocol, commented on the analyses and drafts and seen and approved the final version of the manuscript.

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Availability of data and materials

We plan to compile an anonymised trial dataset with individual participant data and co-ordinate a data dictionary with FOCUS and AFFINITY. The datasets used and/or analysed during the current study could be made available by the corresponding author in response to a reasonable request. However, according to the Swedish Secrecy Act 24:8, an interested researcher must first apply and receive approval from a Swedish REC. 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 and consent to participate

All patients provided written informed consent before randomisation. The study was approved by the Research Ethics Committee (REC) in Stockholm, Sweden on 30 September 2013, number 2013/1265–31/2 (Additional file 3) All seven subsequent amendments (Additional file 3) were approved by the same REC. Details of all amendments and their justification are given in Additional file 4. The date and number for all amendments.

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

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.
PhD students are affiliated to the EFFECTS study.
Currently, we have registered three PhD students for projects associated with the EFFECTS study: Ann-Sofie Rudberg, Eva Isaksson, and Elias Lindvall.

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