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Addition to EFFECTS, reference number 2013/1265-31/2

The undersigned wishes to add to the above application in relation to the EFFECTS study.

We have now carried out the feasibility phase of EFFECTS, and according to the earlier research plan we then planned to evaluate the protocol and make the necessary changes according to the experience obtained.

In order to facilitate the Ethical Review Board's assessment, I have attached both the current version of the protocol (version 4.5, date 15 March 2015) and the patient consent document (version 4.3)

Page numbers refer to version 4.5 of the protocol. New text is marked in red. This text colour will be reverted if the Ethical Review Board approves these additions. The following changes have been made between versions 4.5 and 4.6 of the protocol:

a) Change to patient consent. That the patient consents to us obtaining information from registers on care consumption, and clarification of the side effects.
Reason: This provides more secure data about health economics, while at the same time making things simpler for the study and reducing the burden of questions to patients and relatives.

b) Page 19. Paragraph 1, changed from "more than 7 000 observed" to "up to 6 100 observed patients"
Reason: The pooled number of individuals in EFFECTS, FOCUS and AFFINITY will be a maximum of 6,100 patients.

c) Page 21 paragraph 2.2.2. Addition of using register data. The sentence "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."
Reason: This provides more secure data about health economics, while at the same time making things simpler for the study and reducing the burden of questions to patients and relatives.

d) Page 23, paragraph 1, removal of the sentence "a printed eCRF, and a copy of all forms used. All forms will be possible to download from the trial website."
Reason: It will be possible to print out our eCRF from the website, and we do not therefore deem it necessary to have it in the Investigator Site File.

e) Pages 30-31. The sentence "The total amount of capsules for six months is 186 capsules of fluoxetine 20mg and 186 capsules of matching placebo" is removed. Change number of capsules to 100 (from 107 and 93).

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Removal of “93 capsules + 14 in back-up, total”, change to “100 capsules”
Change from "(93 capsules)” to “(100 capsules)”
Point 9.8.1, remove “in the patient diary”
Reason: Correction to the right number of capsules. Patients do not have any diaries for side effects.

f) Page 35. Adjustment and correction of errors in Table 10.1. STUDY ASSESSMENT SCHEDULE. Addition of time intervals for the various follow-ups.

g) Page 36, 10.2, last sentence of paragraph 1 “The patient and relatives will receive a diary in which they are encouraged to record the date and nature of any adverse events.” is removed.
Reason: Patients do not have any diaries for side effects.

h) Page 36. Under the heading Alert of Adverse Reactions, the following sections are removed: “… 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…”

Regarding the system for event reporting, the sentence: “At these follow ups the GP or other responsible physician will be asked by the local EFFECTS team about adverse events.” is removed.
Reason: We want to simplify the process for the local centre. In order to maintain security, we will encourage patients and relatives to call the local centre 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 physician or nurse.
The reference saying that we will have a special system with pre-stamped envelopes and a web-based solution for patients and relatives is thus omitted.

Under point 10.3, we have re-worded the text so that it corresponds with the follow-up carried out (typographical error in the protocol on this page). We are therefore adjusting the text to: face-to-face follow-up locally at 6 months and additional central follow-up (survey) at 6 and 12 months.
We will not have any web-based follow-up available for patients and relatives.

i) Page 37. Sample size calculation: Minor modification, since the sister study AFFINITY is expected to include 1,600 patients (not 1,500), the total included in the study is adjusted to 6,100 (not 6,000).

The following 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
    - o the enrolment into specific pre-specified subgroups
    - o completeness of follow up
    - o 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.”
Reason: This text is not correct.

j) Page 39. Motor function – NIHSS, speech – NGTA
The following sentence is 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."
Reason: We do not use the Fugl-Meyer Scale or ANELT (typographical error in the protocol on this page).

k) Page 40. Adjustment of the number of EQ5D-5L measurements during the main phase: a reduction from having measured EQ5D-5L during the pilot phase on inclusion on 6 occasions (1 week, 4 weeks, 3 months, 6 months and 12 months) to measuring at 4 measurement points (inclusion, and 3, 6 and 12 months).
Reason for this adjustment: We do not need 6 measurement points for quality of life, and we want to reduce the burden for patients.

l) Page 43, Section 15.3.1, paragraph 3. We are adjusting the wording to make it clearer that SUSAR must be reported via the helpline within 24 hours instead of by fax. The sentence now reads "SUSAR should be reported to the helpline (073-663 74 44) within 24 h".
The sentence "and must sign the EFFECTS trial prescription form for the trial medication." is deleted. Does not apply.

m) Page 52. Clarification that only the most recent version of the research protocol needs to be included in the Investigator Site File. The following sentence is added: "Every center must have the latest version of the protocol in their Investigator Site File."

Changes to the form:
m) Remove identity for MoCA. Reason: Not compatible with GCP.

n) Print-out form: Remove "If there have been changes to the medication at baseline". Medications must instead be listed when printing out the form.
Reason: The previous reasoning was a little unclear. We are making this change to make it clearer and simpler.

o) Changes to "Patient and relative information 18 May 2015 version 3" – clarification of possible side effects of fluoxetine, and request to be able to use register data. Changes to the text are marked in red in the accompanying document. This red marking will then be removed. The text reads:

"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."

Appendices

Current version	**Updated version**
Study Protocol Version 4.5, date 15 March 2015	Study Protocol Version 4.6, date 18 May 2015
Patient and relative information version 4.2 25 April 2013 version 2	Patient and relative information 18 May 2015 version 3

Resource letters from the following hospitals:
Mora General Hospital, Falu General Hospital
Lidköping[1)]/Norrtälje, Kristianstad

Stockholm, date as above

Erik Lundström
Chief Investigator EFFECTS

A fee of SEK 2,000 has been paid via Karolinska Institutet.

Resource letters have previously been submitted for: Danderyd Hospital, Karolinska Hospital (Solna), Hässleholm, Skaraborg Hospital Skövde, Uppsala University Hospital, Karolinska Hospital (Huddinge) and Capio St Göran's Hospital

1) Lidköping refers to "Skaraborg Hospital, Lidköping"

APPROVED 10 June 2015
[signed]
Pär Sparén
Scientific secretary
Regional Ethical Review Board in Stockholm