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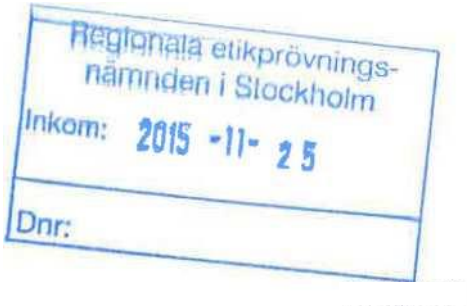
Amendment 3 for the EFFECTS study.



2015/2056-32

Re: EFFECTS ESTABLISHING THE EFFECTS(S) AND SAFETY OF FLUOXETINE INITIATED IN THE ACUTE PHASE OF STROKE

Main application: Ref.: 2013/1265-31/2. Date 30 September 2013
Amendment 1: Date: 15 April 2015
Amendment 2: Ref.: 2015/991-32. Date 10 June 2015

A: As an addition to the previously approved application, the following centres will include patients in the study (resource letters attached):

1. Rehab Station Stockholm
2. Mälar Hospital Eskilstuna
3. Halland Hospital Halmstad
4. Skåne University Hospital Malmö
5. Helsingborg General Hospital
6. Norrland University Hospital Umeå
7. Visby General Hospital
8. Sundsvall Hospital.

APPROVED 30 November 2015
[signed]
Pär Sparén
Scientific secretary
Regional Ethical Review Board in Stockholm

We have previously submitted resource letters for: Danderyd Hospital, Karolinska Hospital (Solna), Hässleholm, Skaraborg Hospital Skövde, Uppsala University Hospital, Karolinska Hospital (Huddinge) and Capio St Göran's Hospital, Mora General Hospital, Falu General Hospital, Lidköping, Norrtälje and Kristianstad.

Clarification in the Research Protocol; updated to version 4.7. After having carried out the pilot phase, we have made certain adjustments to the Research Plan.

B: When it comes to quality of life, the following is stated in our protocol (page 39 in Research Protocol version 4.6)

> Self-reported quality of life will during the pilot phase, measured at baseline, 1 week, patient or proxy), 4 weeks, 3 moths [sic], 6 months, and at 12 months of follow up will be measured using the EuroQoL 5 Dimensions (EQ5D-5L) scale.
>
> In the main phase, EQ5D will be measured at inclusion, at 6 and 12 months follow-up.

After having received a number of questions from participating centres and our monitors, we would like to clarify the sentence about the main phase. First, a little background. We have close cooperation with our sister study FOCUS in Edinburgh. FOCUS measures EQ5D at 6 and 12 months centrally via a survey that is sent to the patient's home. In this follow-up, only the question section of EQ5D is used, not the VAS thermometer (page 2 in EQ5D). The reason for this is that an additional survey – the Stroke Impact Scale (SIS) – includes a VAS thermometer. We have been concerned that the patients would conflate the different thermometers. At the same time, we have been keen to be able to pool data with FOCUS (Edinburgh). This means that in the two central forms, our data and Edinburgh's data are identical, the questions in EQ5D.

At the same time, our ambition has been to make the health economic analysis in Sweden clearer. We have therefore introduced EQ5D on inclusion and at the local repeat visit, at 6 months. Because we wanted it to be possible to compare inclusion with the 6-month check, we used the entire EQ5D instrument, i.e. the 5 questions including the VAS thermometer at:

a) Local measurement of the entire EQ5D on inclusion (not included in Edinburgh)
b) Local measurement of the entire EQ5D at 6 months (not included in Edinburgh)

In order for this to be completely clear, we have made certain changes in 10.1 on page 35 of the Research Protocol. The text marked in red and the figures are stated to highlight what is commented on under the table. We will change the time intervals to months (after 1 week – see the heading row marked in red). Instead of writing 4 weeks, we are now writing 1 month, etc. The figures in the table and the text colour will be removed in the published protocol.