Regional Ethical Review Board in Stockholm

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Karolinska Institutet

Department of Clinical Neuroscience

Karolinska University Hospital, Solna Neurology, R3:04
Erik Lundström
Docent, Section Consultant
erik.lundstrom@ki.se
Tel. +46 (0)707 677 411, +46 (0)8 517 746 97

Regional Ethical Review Board in Stockholm
FE 289
171 77 STOCKHOLM
E-mail: kansli@stockholm.epn.se
Telephone: +46 (0)8 524 870 00

Stockholm, 24 March 2017

Amendment 6 for the EFFECTS study

Approved 28 March 2017
[Signed]
Scientific secretary
Regional Ethical Review Board in Stockholm

EudraCT no.: 2011-006130-16
EPN no.: Ref. no.: 2013/1265-31/2. Date 30 September 2013
Amendment 1: Date: 15 April 2015
Amendment 2: Ref. no.: 2015/991-32. Date 10 June 2015
Amendment 3: Ref. no.: 2015/20156-32. Date 30 November 2015
Amendment 4: Ref. no.: 2016/1191-32. Date 14 June 2016
Amendment 5: Ref. no.: 2016/2531-32). Date 4 January 2017

As an addition to the previously approved application, resource letters are submitted for:

1. Dalen Hospital and Lindesberg General Hospital. For reference, we have changed the PI at Skövde from Erik Bertholds to Björn Cederin, and at Karolinska Hospital Huddinge from Ioanna Markaki to Maria Lantz. This has been updated in the delegation lists.

Additional centres that may be included during 2017 are: Hudiksvall, Kalmar, Eksjö, Värnamo, Östra Hospital, Borås, Sunderby Hospital, Skellefteå, Karlstad, Södertälje, Kullbergska, Jönköping, Karlskrona, Karlshamn and Varberg.

We have previously submitted resource letters for: Danderyd Hospital, Karolinska Hospital (Solna), Hässleholm, Skaraborg Hospital Skövde, Uppsala University Hospital, Karolinska Hospital (Huddinge), Capio St Göran's Hospital, Mora General Hospital, Falu General Hospital, Lidköping, Norrtälje, Kristianstad, Rehab Station Stockholm, Mälar Hospital Eskilstuna, Halland Hospital Halmstad, Skåne University Hospital Malmö, Helsingborg General Hospital, Skåne University Hospital Lund, Norrland University Hospital Umeå, Visby General Hospital, Sundsvall Hospital, Sahlgrenska Hospital, Gothenburg, Högsbo Hospital, Gothenburg, Stora Sköndal, Östersund Hospital, Alingsås Hospital, Ängelholm Hospital, Stockholm Nursing Home, Örebro University Hospital Rehabilitation Medicine Clinic, Norra Älvsborg

Translated by
Språkservice
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Major amendments, updates in the Research Protocol to version 4.9

1. Our primary outcome measure is an ordinal scale called the modified Rankin Scale (mRS). The scale, which goes from 0 (no symptoms) to 6 (dead), is the most common outcome measure for stroke. The mRS is most commonly carried out at a repeat visit, but it can also be done by telephone or via a survey. Carrying out surveys during repeat visits can be time-consuming, particularly in the case of large studies, and our colleagues in Edinburgh have therefore developed a scale called the *simple modified Rankin Scale questionnaire* (smRSq). This consists of five questions, and can be carried out as a survey or by telephone. smRSq is validated in English, but not in Swedish. In our research plan, we stated that we planned to carry this out during 2013 – see below. However, because we have been forced to focus on other issues (preparing randomisation systems, eCRF, inclusion of patients in the study), we have not been able to carry out the planned study. Since several years have passed since we applied, we believe that it is important to clarify our position on this matter to the Ethical Review Board.

   We wrote the following in version 4.8 of the research plan, on page 22. The wording remains unchanged since the first application, which was approved on 30 September 2013:

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

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

   Any misclassification of patients into an inappropriate mRS category may reduce the power of the trial. To minimize misclassification and intermodality differences we will use the simple modified Rankin Scale questionnaire (smRSq) described by Bruno and colleagues. This has been delivered by both telephone and postal questionnaires and has been completed by patients and proxies (Bruno 2010, 2011) (Dennis 2012) (Lundström in early manuscript 2013)."

   What we now intend to do is to investigate whether the survey that we sent out at 6 and 12 months gives similar results compared with a traditional assessment during a repeat visit.

   This does not involve any additional burden for the patient compared with how we do things now. Every participant in the study already answers the five questions that form the basis for smRSq. What is being added is a number of physicians and nurses carrying out a traditional assessment of mRS at the 6 month repeat visit.

   All the information required in order to carry out a regular mRS is obtained during the ordinary repeat visit. I have personally tried out doing this at a number of repeat visits, and it does not make the repeat visit any longer or more difficult for the patient.

However, since the planned comparison between smRS and mRS has not yet been carried out, we would like to apply with this amendment to carry out the sub-study.

This will affect a total of 65 individuals.

The method for carrying out a study within a study is called *Study Within A Trial* (SWAT) in English (Anon 2012). We intend to register this study in a register called the Northern Ireland Hub for Trials Methodology.

The changes in version 4.9 of the research plan are marked in red below:

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

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

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

Synopsis of manuscript with preliminary title: *Agreement of the Swedish small modified Rankin Scale questionnaire with face-to-face modified Rankin Scale*

The smRSq is sends [sic] to patients by the Trial Manager Assistant (TMA) at 6 and 12 month post randomisation. If the patient does not answer, the TMA contacts the patient by phone and reminds them to send in the questionnaire. If they have difficulty answering for themselves TMA helps them fill in the form by phone.

Statistics

Number of patients

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

Statistical methods and data management

Statistical comparisons in order to test differences between dependent observations will be made by use of pair-wise Student's t-test for correlated means and statistical comparisons between two independent groups will be made by use of the Student's t-test for uncorrelated means., [sic] 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.

A fee of SEK 2,000 will be paid, stating the reference:
Amendment 6 EFFECTS/Lundström

Erik Lundström
Chief Investigator EFFECTS

Appendices:
Copies of Resource certification for new centres
EFFECTS Protocol version 4 9 EU no. 2011-006130-16

References

Anon. Education section - Studies Within A Trial (SWAT). Journal of Evidence-Based Medicine 2012; 5(1): 44-5

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Bruno A, Akinwuntan AE, Lin C, Close B, Davis K, Baute V, Aryal T, Brooks D, Hess D, Switzer J, Nichols F. Simplified Modified Rankin Scale Questionnaire: Reproducibility Over the Telephone and Validation With Quality of Life. Stroke. 2011;42:2276-2279.

Dennis M, Mead G, Doubal F, Graham C. Determining the modified Rankin score after stroke by postal and telephone questionnaires. Stroke 2012; 3:851-3

van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988 May;19(5):604-7