Emotional and cognitive determinants of post-stroke fatigue. A prospective study.

1.1 PROJECT SUMMARY
The purpose of this study is to obtain new knowledge about post-stroke fatigue, with the aim of providing better health-care to patients after stroke. Studies show a prevalence of fatigue in stroke-survivors ranging from 25% to 91% [1-3]. One year after stroke, a quarter experience fatigue as the most difficult problem to cope with [4], and patients, caregivers and health-care professionals rate fatigue as one of the 10 most important areas of research after stroke [5].

Fatigue is not routinely assessed, and causes and associations are not completely understood [2, 6, 7]. We want to study the association between fatigue and cognitive functions such as attention, memory, processing speed, and executive functions (i.e., problem solving ability). This association has been scantly assessed in the chronic phase after stroke, and existing studies have conflicting results [4, 8, 9]. The significance of emotional factors which are often highlighted in models of fatigue [1, 10, 11] will be studied prospectively. The potential benefit of this study is significant. Metacognitive thinking style, or how one relates to one’s thoughts and emotions, is a possible focus for treatment, but as of yet, no studies have linked post stroke fatigue and metacognitive coping style. Some studies suggest that cerebral motor function is relevant to fatigue [12, 13]. Our study will control for degree of activity as measured by modern technology.

The patients included in this study are the Norwegian cohort of the study “Rehabilitation, function and quality of life after cerebral stroke in North Norway and Denmark”. Data collection for the first year after stroke is completed. This new study will consist of a follow up of Norwegian participants 3 years after stroke and includes assessment of neuropsychological function, fatigue, activity and quality of life. The study is supported by relevant user representatives and is in line with prioritized research areas in the Northern Norway Regional Health Authority strategy 2016-2020.

1.2 BACKGROUND AND SIGNIFICANCE
Fatigue and cognitive function
Cognitive impairment may result from brain injury of a range of different etiologies, and neuropsychological tests are used to assess neurocognitive function. Reduced cognitive functioning can affect activities of daily living and employability without there being other visible loss of function. Few studies have applied valid and reliable neuropsychological tests when examining the relation between cognitive function and post-stroke fatigue, and studies are often small [4, 8, 9, 14].

Radman et al. (2012) examined 99 patients with mild stroke 3 and 12 months after stroke, and found that those with fatigue had significantly lower scores on tests of attention and executive function, but not on memory tests. After controlling for concurrent depression, the association between fatigue and reduced executive function remained [4]. Pihlaja et al. (2014) examined 33 patients 3, 6, and 24 months post stroke, controlling for depression. Patients with fatigue showed significantly lower processing speed at 3 and 6 months, and reduced memory at 6 months. Pihlaja found no association between executive function and presence of fatigue [9]. Johansson et al. [14] examined young patients aged 18 to 50 on average 8 years after stroke. They found a significant association between fatigue and slower processing speed, while there was no correlation between fatigue and other cognitive domains. Johansson and Rönnbäck [8] reported, in a Swedish study examining 24 patients in the chronic phase after stroke, a significant association between fatigue, processing speed and attention. Limitations in this study were a small sample size and not controlling for
depression. We have only encountered one study conducted at an interval 2 years post stroke, and this showed no significant association between cognitive impairment and fatigue when controlling for concurrent depression [9].

Three reviews from 2014 and 2015 concluded that stroke-related impairment of executive function (planning, reasoning, problem solving), attention and processing speed were associated with fatigue in some studies, but this still needs to be confirmed [6, 7, 15]. Some have also found an association between fatigue and impaired memory [9], while several studies fail to replicate this.

In summary the significance of cognitive impairment in relation to fatigue is poorly understood, both when it comes to cognitive profile and the impact of depression. Fatigue after stroke appears to be stable over time [3, 4, 16-18]. The natural recovery of cognitive function after stroke appears to plateau and stabilize after 1-2 years [19], and neuropsychological assessment should thus be done long term after stroke [19].

Emotional factors, coping strategy and fatigue
The emotional factors depression and anxiety are prevalent in stroke survivors [20]. It is not clear whether emotional symptoms play a causal role in the development of fatigue [15, 21]. In a review [21], only one study had examined the temporal relationship between fatigue and emotional factors. This study showed that presence of depression and/or anxiety 2 months post-stroke predicted fatigue 18 months after stroke [10]. A meta-analyses from 2014 [15] showed a significant association between fatigue and depressive symptoms and a trend towards an association between fatigue and anxiety. Several studies have found that fatigue can be present independently from depression [22-24]. It is currently not clear whether depression is a predictor of post-stroke fatigue.

Having a stroke is a life-changing event due to loss of function, grief, and concern for one's health and the manner of coping is important to the presence, and maintenance, of emotional symptoms. Due to small sample sizes and conflicting results in previous studies [6, 25-28] the association between coping style and fatigue is not yet clear. Metacognitions predict symptoms of fatigue in Chronic Fatigue Syndrome (CFS) [29], but this relationship has not been examined in post-stroke fatigue. Metacognitive therapy [30] focuses on how one relates to and thinks about one’s own thoughts and feelings. It is based on the metacognitive model, which proposes that a thinking style dominated by rumination, worry and threat monitoring maintain emotional distress. Increased knowledge about metacognitions in persons with post-stroke fatigue may open the door to new psychological interventions using metacognitive therapy.

Fatigue and health-related quality of life
In patients with adequate neurological and neuropsychological recovery after stroke, fatigue may still negatively affect psychosocial and occupational life [24]. Staub and Bogousslavsky [24] question whether persons with smaller neurological and cognitive sequelae after stroke experience fatigue as more disabling than persons with larger functional impairment, because people with less impairment are subject to higher societal demands. There are few high-quality studies examining the association between fatigue and quality of life. Two studies show reduced quality of life in patients with fatigue [31, 32]. This association has often been studied using generic health-related quality of life instruments, which to a lesser extent capture stroke-specific functional impairment [33]. The questionnaire Stroke-Specific Quality of Life Scale (SSQOL) [34] however, assesses 12 stroke related domains, and is thus well suited for investigating health-related quality of life after stroke.
We have only been able to find one study [32] that examined stroke-specific quality of life associated with fatigue long term after cerebral stroke. Results revealed significant differences between participants with and without fatigue 2 years after stroke on 7 out of 12 domains [32]. Our study aims to examine whether fatigue independently impact reduced quality of life after stroke, and if the important associations found in Chen, Qu [31] can be confirmed in a new study when applying the 12 domains covered in SSQOL [31].

**Stroke-related and demographic variables (covariates)**

A number of variables need to be controlled in this study. The underlying neurobiological mechanisms associated with the development of fatigue are unclear [2, 6, 7]. A systematic review found no association between fatigue and white matter lesions, cerebral atrophy, type of stroke (ischemic or hemorrhagic), nor the location of the brain affected (defined clinically or radiologically) [2]. Most studies find no association between fatigue and demographic factors, such as educational level and marital status, although one review found a slightly higher prevalence of fatigue in women and older patients, and in persons with reduced occupational participation [6]. In accordance with Duncan, Lewis [35] we have chosen to control for pre-stroke fatigue, in addition to relevant stroke specific and demographic variables (see Table 1). Because low physical activity predicts pre-stroke fatigue [35], physical activity will be measured and controlled in the present study.

**Potential benefits for patients and health care services**

We expect this study to yield new and important knowledge about factors associated with fatigue, or predictors associated with the development of fatigue after stroke. In turn, this may lead to prevention as well as development of better-suited treatment and rehabilitation methods after stroke.

**Study objective, specific aims, hypotheses**

The main purpose of this study is to uncover new knowledge about fatigue long-term after cerebral stroke, related to cognitive and emotional factors, coping strategies and health-related quality of life.

**Research question 1**

What specific cognitive domains (attention, speed of information processing, memory, executive function) are related to presence of fatigue 3 years after cerebral stroke?

Hypothesis: We expect higher levels of fatigue to be significantly associated with reduced executive function, attention and processing speed, but not with memory functions.

**Research question 2**

Do symptoms of anxiety and depression 3 or 12 months after stroke predict presence of fatigue long-term (3 years) after stroke?

Hypothesis: We expect subclinical or clinical levels of depression early after stroke (3 and 12 months) to be associated with fatigue long term (3 years) after stroke.

**Research question 3**

Are metacognitions associated with post-stroke fatigue?

Hypothesis: We expect persons with a metacognitive thinking style dominated by rumination, worry and threat monitoring, to have higher occurrence of fatigue, and persons with a low degree of rumination and worrying to have a lower degree of fatigue. A metacognitive thinking style adopting a low degree of rumination and worrying will weaken a positive association between depression and fatigue.

**Research question 4 (PhD-candidate is co-author)**

What domains of stroke specific quality of life, measured with the questionnaire Stroke Specific Quality of Life 3, 12 and 36 months post stroke covariate with long term (3 years)}
Hypothesis: Fatigue long term after stroke covariate with poorer stroke-specific quality of life overall, and with the domains Mobility, Mood, Thinking, Personality, Energy, Family roles, and Social roles; at all three time points applying SSQOL.

Choice of method
The research questions listed above are examined using quantitative methodology in a prospective observational study of a cohort of patients with cerebral stroke. The study is a continuation of an ongoing study: Patients with cerebral stroke were included from stroke units at UNN in the period March 2014 until 2015. Data collection 12 months after stroke was completed January 2017, and results are being published (2 articles have been submitted, 2 in manuscript, 2 planned). Conduction this follow up study 3 years after stroke, with neuropsychological testing, measurement of activity and questionnaires, will secure optimal utilization of data. Question 1 and 3 are examined satisfactorily in a cross-sectional study 3 years after stroke, controlling for covariates. Question 2 and 4 are tested prospectively. Results will be analyzed with appropriate statistical analyzes (see Statistical analyzes p.6).

Methods
Study population:
From March 2014 through December 2015 all patients undergoing acute cerebral stroke admitted to a stroke units at the University Hospital of North Norway (UNN) were prospectively included in a multicenter cohort study, “Rehabilitation, function and quality of life after cerebral stroke in North Norway and Denmark (2013/1472/REC North)”. Exclusion criteria were non-verified cerebral stroke, residing outside the study area, and serious illness/comorbidity preventing registration in the Norwegian Stroke Register. Of about 400 included, 280 participants responded to the questionnaire, "Life after stroke" at 3 months after stroke. Follow-up 12 months after stroke were completed at the turn of the year 2016/17, including more than 250 participants. These 250 individuals, having participated at 3 and 12 month after stroke, are eligible for the present study. Mean age at time of stroke was 70 years. Neuropsychological assessment will be restricted to those under 75, due to increased probability of age-related cognitive decline in the highest age groups. One hundred and fifty participants will be included in the questionnaire-based examination only, and 100 of these will undergo neuropsychological assessment.

Variable overview: Table 1 (page 10) displays variables obtained in the acute phase after stroke and at 3 and 12 months, and to be retrieved at 3 years post stroke.

Data already collected: Data at 3 and 12 months after stroke are registered, and include: From the Norwegian Stroke Register: Demographic characteristics, comorbidity and smoking status, type of stroke and stroke diagnosis, degree of disability/dependence after a stroke (Modified Rankin Scale) at 3 months. At 3 and 12 months after stroke: occupational status, health-related quality of life (SSQOL), and emotional symptoms/distress (Hospital Anxiety and Depression Scale) (HADS).

Data to be collected in the present study 3 years after stroke: Measures of Degree of disability/dependence (Modified Ranking Scale), health-related quality of life (SSQOL) and emotional symptoms/distress (HADS) are repeated. In addition, fatigue (Fatigue Severity Scale - FSS, Chalder Fatigue Questionnaire - CFQ), metacognitions (Metacognitions Questionnaire - MCQ-30) and neuropsychological function will be measured. Cognitive functioning will be assessed with standardized neuropsychological tests. All neuropsychological evaluations will be conducted or supervised by neuropsychologists and documented in the patient's medical records. When required by the participant, a copy of the
A neuropsychological report will be provided to the patient and GP. Activity measures lasting 7 days will be carried out for participants undergoing neuropsychological testing. The study will be registered in ClinicalTrials.gov.

**Measurements:**

**Fatigue:** Self-report inventories in which the patient indicates presence and degree of fatigue are recommended for the assessment of fatigue [2]. In a review article, the Fatigue Severity Scale (FSS) [36] was the most commonly used questionnaire for stroke survivors [37-39]. FSS is translated to Norwegian [40], and includes 9 items related to fatigue graded on a 7-point Likert-like scale ranging from 1 ("disagreeable") to 7 ("highly agreeable"). The average score for all 9 items constitute the FSS score. The most commonly used operational definition of fatigue is FSS ≥ 4.0 points [3, 26, 41], and will be used in the present study.

Another widely used instrument is the Chalder Fatigue Questionnaire (CFQ) [42]. CFQ has a Norwegian translation, and normative data for the Norwegian population [43]. CFQ is, as far as we know, not validated in a stroke population. This will be done in a substudy not included in the actual doctoral project. In line with Duncan F. et al., pre-stroke fatigue is assessed with the question: “Did you have a problem with fatigue before your stroke?” [35].

**Neuropsychological assessment:** Testing is completed over 2 hours including breaks. Assessment includes a standard cognitive examination, as well as additional focus on cognitive domains found to be related to fatigue in previous studies [7, 44]. The following tests will be applied (references refer to published manuals, or published research using or evaluating the tests): Matrix Reasoning, Vocabulary, Digit Span, Coding (WAIS-IV) [45]; Trail Making Test; Stroop Interference Test; Word Fluency Test (these three are included in the D-KEFS test battery) [46, 47]; Lafayette Grooved Pegboard Test [48]; Connors Continuous Performance Test-III [49]; California Verbal Learning Test II [50, 51]; Rey-Osterrieth Complex Figure Test [52]; Behavioral Rating Inventory of Executive Function-Adult Version [53]. All tests are widely used internationally, and have validated Norwegian translations.

**Health-related quality of life:** Stroke Specific Quality of Life Scale (SSQOL). The original SSQOL [34] questionnaire consists of 49 items covering 12 domains: Mobility, Energy, Upper Extremity Function, Work and Productivity, Mood, Self-Care, Social Roles, Family Roles, Vision, Language, Thinking and Personality. Each domain is measured by three to six items using a 5-point (1–5) Likert scale (higher scores indicate better function). Satisfactory test-retest reliability and internal consistency has been established. A Norwegian translation of SSQOL has recently been published [61]. Results form the SSQOL 3 years after stroke will be used in the present study.

**Emotional symptoms/distress and coping:** Hospital Anxiety and Depression Scale (HADS) consists of 14 items that assess non-vegetative symptoms of depression (7 items) and anxiety (7 items) [54, 55]. The questionnaire is already included at 3 and 12 month follow-up, and will be repeated in the present study 3 years after stroke. The HADS has been used as a screening tool in several languages and is particularly suited for hospital populations, including persons with stroke [56]. It uses a response scale of 0–3 (higher is worse). Subscale sum scores range from 0 to 21, and a cut-off score of 8 - 10 indicate possible (subclinical) anxiety or depression, while scores of 11 and higher indicate probable (clinical) anxiety or depression. The total HADS score (range 0–42) can additionally be considered a global measure of psychological and emotional distress.

The Metacognitions Questionnaire (MCQ-30) is a 30-item self-report inventory for assessing metacognitions [57]. The items are scored on a four-point Likert-type scale ranging from 1 (I do not agree) to 4 (I totally agree), allowing a range from 30 to 120. Higher scores indicate more dysfunctional metacognitions. Five subscales exist: Positive beliefs about worry (e.g.,
‘Worrying helps me to solve problems’), Negative beliefs about worry (e.g., ‘When I start worrying I cannot stop’), Cognitive confidence (e.g., ‘I do not trust my memory’), Need for control (e.g., ‘It is bad to think certain thoughts’) and Cognitive self-consciousness (e.g., ‘I monitor my thoughts’). MCQ-30 has good psychometric properties [58].

**Demographic characteristics:** Age at time of injury, gender, marital status (married/cohabitant/widowed/single), education level (years), work status at 3 months after stroke and now (student/unemployed/working full-time or part-time/retired/sick-leave).

**Stroke characteristics:** Previous stroke, stroke subtype (stroke diagnosis according to ICD-10 (I63 Cerebral infarction, I61 Intracerebral haemorrhage, I64 Stroke, not specified as haemorrhage or infarction), lateralization of stroke, comorbidity, degree of disability or dependence in activities of daily living (ADL) measured with the mRS. The mRS ranges from 0 to 6 (‘perfect health to death’) and is widely used internationally throughout hospital services [59].

**Physical activity:** Measured with Axivity AX3 accelerometers. The same procedure as used in the UK Biobank Study [60] will be followed. Each participant has an accelerometer on both wrists over a period of 7 days. Average acceleration and time spent in continuous periods of 5 or 10 minutes moderate or hard physical activity will be used in analyzes.

**The primary outcome measure** of this study is presence of post-stroke fatigue defined as score ≥ 4 on the questionnaire Fatigue Severity Scale. Secondary outcome is stroke-specific quality of life (SSQOL). Explanatory variables are specific domains of cognitive function measured with neuropsychological tests, symptoms of anxiety/depression (score above cut-off) (HADS), as well as trajectories of emotions assessed at 3 and 12 months and 3 years after stroke. Metacognitive coping strategy is treated as a possible mediator for the association between depression/anxiety and fatigue.

**Statistical analyses and power analyses:** Descriptive data will be presented as means, standard deviations, and ranges or as proportions. Correlations will be examined using Pearson r/Spearman rho or chi-square (or Fisher’s exact) tests to compare continuous or dichotomous data, respectively. Logistic regression analyses will be used for binary outcomes. One example is analyses of the relationship between cognitive test results and fatigue, defined as a clinical or dichotomous variable, i.e. 0 - no fatigue, or 1 - clinical fatigue (FSS≥ 4.0), and neuropsychological test scores defined as independent variables. Neuropsychological test scores will be treated as continuous variables. Logistic regression will also be applied in analyses of the relationship between HADS scores at 3 and 12 months after stroke as independent variables and fatigue, controlling for covariates. Temporal changes in emotional symptoms (ie anxiety and depression) are examined with mixed model regression analyses. Mixed models are better suited when analyzing data that are non-independent and longitudinal/repeated, and better at dealing with missing values compared to traditional regression methods.

**Power analyses and sample size estimation:** Based on a previous study [4], which showed an OR = 3.0 for the relationship between cognitive tests and fatigue, a sample size of 32 will obtain an estimated power of 78% at p = .05 and an estimated multiple R-sq of 20% between predictors. A number of possible predictors (age, gender, type of stroke, baseline mRS, education level, pre-stroke fatigue, anxiety, depression, activity level), should be controlled for in the present study, thus increasing the sample size. With 10 persons per variable, we need at least 80 participants. Taking withdrawal and missing data into account, at least 100 participants will be recruited to neuropsychological assessment, and 150 will be recruited to answer questionnaires only.
Duration of the project, project management, organization and collaboration

Detailed timeline with main activities and milestones is described in the grant application. The PhD candidate will join the position on 01.02.2018. Recruitment will start in May 2018, when ethics approval is completed (REC North), and recruitment and enrollment will continue through 2018. We apply for PhD funding over 3 years starting 01.02.2018. The research group is an interdisciplinary team with the necessary qualifications and resources to complete the study, including specialized clinical and scientific expertise in rehabilitation after stroke, neuropsychological qualifications, and representatives from user groups.

Clinical neuropsychologist Mari Thoresen Løkholm will be the PhD candidate in this project. Løkholm is employed at the Department of Rehabilitation at the University hospital of North Norway (UNN), and has 14 years of experience as a clinical psychologist/neuropsychologist working with stroke survivors. The project manager/principal investigator is dr. med, professor Audny Anke who is also the main supervisor. Professor Anke is employed at the Department of Rehabilitation at UNN and at UiT The Arctic University of Norway. She is also the principal investigator and supervises two other PhD candidates in the multicenter study mentioned above. She has considerable scientific experience from rehabilitation studies and in relation to patient groups with cognitive problems. The second supervisor is postdoc and neuropsychologist Marianne Halvorsen, UNN. Halvorsen has considerable scientific experience from studies on mental disorders and cognition. National collaborator is professor Marit Kirkevold, head of “The Research Center for Habilitation and Rehabilitation Models and Services” (CHARM), University of Oslo (UiO), has extensive research experience relevant to the study of post-stroke fatigue, and has conducted earlier [16] and ongoing studies on fatigue and coping after cerebral stroke. International collaborator with extensive scientific experience is professor Jørgen Feldbæk Nielsen, Head of Research at Hammel Neurocenter, Denmark. The study will be conducted at the neuro-rehabilitation unit at UNN, and is supported by Head of Staff Christoph Schäfer, and Head of Division Bjørn-Yngvar Nordvåg.

Other collaborators: Professor Oddgeir Friborg, at the Department of Psychology, UiT will contribute to the project with general scientific and statistical competence. Associate Professor Gunn Pettersen, Head of the research group at UiT, and Associate Professor Gyrd Thrane, have given important contributions to the protocol and will contribute to manuscripts. Gyrd Thrane has scientific expertise in physical activity measures. The PhD students physiotherapist Synne Garder Pedersen and senior consultant Guri Heiberg will also contribute to manuscripts, having detailed knowledge of collected data and measurements. Bjørn Bjørnstad and Melissa Birkeland in LHL - The National Association for Heart and Lung disease represent stroke survivors (see section 1.3) in this project.

Completion of the project: The PhD student is active and proficient, is supported by hospital officials, and will enter an already competent research group. Data collection (neuropsychological testing) will be carried out in collaboration with psychology students at UiT The Arctic University of Norway as well as with other members of the research group. The PhD candidate will be the first author of 3 and co-author of 1 article.

Budget: Budget information is described in the grant application.

1.3 USER REPRESENTATIVES

In the present context, users are stroke survivors and persons representing them. This project is warmly supported from members in LHL - The National Association for Heart and Lung disease. Representatives are Bjørn Bjørnstad, chairman of LHL Tromso, and Melissa Birkeland in LHL network for young stroke survivors. User representatives are included as advisors and collaborators in the project. They will take part at meetings discussing study recruitment and results. Collaboration with users is also important when spreading results through non-academic channels/forums. Furthermore, users may help communicate study
results beyond academic settings and scientific journals, and can help highlight the need for more suited, or new, treatment methods. Results from this study as well as knowledge of fatigue will be communicated through popular science articles and oral presentations.

1.4 STRATEGIC ANCHORING AND CENTRAL PERSPECTIVES

**Strategic anchoring:** Consequences of cerebral stroke is an important research area at the Department of Rehabilitation/University Hospital of North Norway. The project application fulfills several priority areas of the Northern Norway Regional Health Authority research strategy for 2016-2020.

**Benefits to society:** Stroke survivors often face many years living with disabilities. Fatigue is a frequent and prolonged sequela, negatively influencing activities of daily living and quality of life. The present study will provide new knowledge about factors associated with the development of fatigue. This may enable early identification and counseling to patients with post-stroke fatigue, as well as development of new interventions. A slight reduction in the occurrence or consequences of fatigue after stroke will be of great importance individually and socially.

**Innovation:** If cognition is associated with fatigue, new interventions in the form of neuropsychological rehabilitation may prove to alleviate fatigue as well. Given an association between anxiety and/or depression and fatigue, mediated by coping strategies, psychological interventions designed to treat emotional distress and improve coping may provide useful in the treatment of fatigue. The rehabilitation process may, in turn, be shortened.

**Environmental impact:** The project does not present any risk to humans or the environment.

**Ethical considerations:** The study will be conducted in accordance with the Declaration of Helsinki (DoH) and approval of the National Committee for Medical and Health Research Ethics in Norway (REC North), and will be presented to the data protection officials at the University Hospital of North Norway (UNN). Informed consent will be obtained to participants through written mail. All data are anonymized, and identification of individuals will not be possible in oral or written presentations of results. Participants will receive an inquiry to participate in this study. Feedback on results will be given to each participant, and referral to relevant health services will be provided when required.

1.5 COMMUNICATION AND DISSEMINATION OF FINDINGS

Results will be presented to healthcare providers at local and national meetings, and at international conferences. The group of researchers in this study are university and hospital employees, and are expected to communicate results to students and colleagues. Data processing will be done by the PhD student in cooperation with supervisors and study collaborators, and published in peer-reviewed journals. The study is conducted in collaboration with LHL - The National Association for Heart and Lung disease. All findings will be presented to healthcare providers and stroke survivors in cooperation with LHL.

**Articles:** The PhD student will be first author of article 1-3, and co-author of article 4:

1. The association between cognitive functioning and fatigue long-term post-stroke. A cross-sectional study with neuropsychological tests.
4. The association between fatigue and health-related quality of life. A prospective study.

**Attachments:** Table 1 (page 11)
References


**ATTACHMENT. Table 1. Variable**

Variables collected in the acute phase, at 3 and 12 months, and variables to be collected in the present study 3 years after stroke. Grey markings are data from the Norwegian Stroke Registry.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Acute. Stroke registry.</th>
<th>3 months</th>
<th>12 months</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
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<td>Chain of Treatment: Debut of symptoms, time of hospital submission, submitted to a stroke unit.</td>
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<td>Comorbidity and smoking</td>
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<td>Type of stroke (CT-skan), lokalization of stroke.</td>
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<td>Stroke diagnosis (ICD-10): I63 Cerebral infarction, I61 Intracerebral haemorrhage, I64 Stroke, not specified as haemorrhage or infarction.</td>
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<td>Discharge: Discharge location.</td>
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<td>Disability/dependence in ADL: Modified Rankin Scale (0-6).</td>
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<td>Smoking status</td>
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<td>Work status at time of stroke and now.</td>
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<td>X</td>
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<td>Stroke Specific Quality of Life (SSQOL).</td>
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<td>Emotional symptoms/distress (HADS).</td>
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<td>Fatigue (FSS and CFQ).</td>
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<td>Coping strategy (MCQ-30).</td>
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<td>Pre-stroke fatigue, one question [35].</td>
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<tr>
<td>Physical activity, 7 days.</td>
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