

Study protocol

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NCT:

Lifestyle change and health behaviour in patients with minor stroke and transient ischemic attack: A randomized controlled feasibility study

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**Nordsjællands
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**KØBENHAVNS
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1 Summary

1.1 Objective

Stroke is a significant cause of morbidity, mortality, and loss of independence worldwide. In Denmark 12,000 people have a stroke per year. About one fourth of patients admitted with a stroke have had previous strokes or TIA. The risk of recurrent stroke is highest in the first weeks and decreasing with time.

Hypertension is one of the leading risk factors for vascular diseases, including stroke and TIA, and lowering of the blood pressure is therefore an essential part of stroke treatment. Smoking cessation, physical activity, and adherence to antihypertensive and antithrombotic medication is highly recommended in patients with minor stroke and TIA.

The objectives of this study are 1) to test the feasibility of a lifestyle and behavioural intervention in a clinical setting, and 2) to test the effect of the intervention on blood pressure in patients with minor stroke and TIA.

1.2 Target and study population

The study will include patients with acute minor stroke or TIA who are discharged to their own home. Patients with prior disability, severe communication problems, severe psychiatric disease, or alcohol abuse will be excluded.

1.3 Methods

1.3.1 Study design

The study will be a randomized controlled feasibility trial. Participants (n=40) will be randomly allocated to either an early initiated counselling intervention with frequent follow-up sessions in 12 weeks, or usual care.

1.3.2 Exposures and outcomes of interest

Participation rate and adherence to the treatment program will be the primary outcome measures of feasibility. Systolic blood pressure will be the primary outcome measure of effect.

1.3.3 Recruitment

Participants will be recruited from admissions to the Department of Neurology at Nordsjællands Hospital, Hillerød.

1.3.4 Statistical analyses

Student t-test will be used as significance test for differences in blood pressure between the treatment groups.

1.4 Expected results

We expect to estimate the participation rate and variance of the blood pressure. These estimates will be used in planning a future randomized controlled trial.

1.5 Discussion

The greatest challenge will be the participation and retention of the participants throughout the study period.

2 Background

Stroke is a significant cause of morbidity, mortality, and disability, both in western countries and globally (1). In Denmark the incidence is around 12,000 per year (2). The life expectancy of patients with stroke and transient ischemic attacks has increased during the last few decades. As a consequence of this the risk of recurrent stroke and other cardiovascular disease has increased. Interventions to reduce the risk of stroke recurrence are therefore needed.

Approximately one in four patients with stroke have recurrent stroke. The risk of recurrent stroke is greatest closest to the incident stroke. Within the first year 12-13 percent have recurrent stroke and after the first year the recurrence rate is 5-6 percent per year (3). Recurrent stroke is an independent risk factor for loss of function, institutionalization, and death (4).

The most important risk factor for stroke is arterial hypertension. Not only does it increase the risk of stroke considerably, it is also highly prevalent in the general population. Other lifestyle factors, such as smoking, physical inactivity, unhealthy eating habits, and abdominal obesity also contribute to the risk of stroke (5).

Preventive medication is an important part of the secondary and tertiary prevention in patients with stroke and TIA. Most of the patients get prescriptions for antithrombotic drugs or drugs to reduce their blood pressure or blood lipids (6). Several studies have found that a substantial part of the patients discontinue the drug treatment over time (7).

2.1 Literature review

Previous research has attempted in different ways to change health behaviour with the aim of preventing recurrent strokes and other cardiovascular diseases in stroke survivors.

The results of previous studies have been varying and it is therefore difficult to point out any specific interventions or element of interventions which would be feasible to implement in clinical practice. Lawrence *et al.* (8) found in a systematic review of 20 randomized controlled trials that multimodal behavioural interventions had a beneficial effect on especially blood pressure. In a similar study Deijle *et al.* (9) found that lifestyle interventions had greater effect if the intervention contained elements of physical activity. On the contrary Lager *et al.* (10) found in a systematic review of 26 randomized controlled trials that interventions aiming at reducing the risk of cardiovascular events in stroke patients had no significant effect.

The time of inclusion in the previous studies has varied quite a lot. In some studies the participants were included within 1-2 weeks after the stroke and in others participants were included until almost two years after. It has been hypothesised in other patient groups that the time just after the diagnosis constitutes a certain *window of opportunity*; a limited period of time in which the patient is particularly receptive of information and behavioural changes (11).

2.2 Justification

In the last decades there has been an increased focus on the importance of health behaviour in the public and among patients in relations to prevention of vascular diseases. There is solid scientific evidence of the harmful effects of lifestyle factors, such as smoking, physical inactivity, and alcohol overuse. But we still lack knowledge about how to disseminate this evidence to the public and how to help and support patients in making suitable choices to prevent recurrence and progression of their disease.

A particularly perspective in this context is the considerable increase of the stroke burden we have seen in low- and middle income countries, which is attributional to the changes in life expectancy, life style, and living conditions. Previously stroke and other vascular diseases were considered diseases of

affluence; now 75 percent of all strokes occur in low- and middle income countries. This change from infectious diseases being the primary burden to non-communicable diseases is in many ways positive, but is also a great challenge. We need to focus our research on treatments which are effective and inexpensive.

2.3 Relevance

This study will contribute with new knowledge about how patient counselling can be conducted in clinical practise and its effect on the patients' risk of recurrent vascular disease after stroke or TIA. The intervention tested in the study will be implemented in current clinical practise and thereby have a direct effect in the secondary and tertiary prevention of strokes.

2.4 Feasibility

Each year the Department of Neurology at Nordsjællands Hospital admits approximately 650-700 patients with a confirm stroke and 200 patients with TIA. Of the patients with stroke 60-65% have a Scandinavian Stroke Scale between 45-58. It is therefore expected that around 600 patients each year will fulfil the inclusion criteria. It is uncertain how many of the patients will meet the exclusion criteria.

3 Purpose, Objectives and Hypothesis

3.1 Purpose of the study

The overall purpose of our research is to develop effective and clinically feasible interventions to prevent recurrent strokes in patients with minor stroke and transient ischemic attacks.

3.2 Objectives

The aim of this study is

- 1) to evaluate the feasibility of a client-centred patient counselling intervention focused on smoking cessation, physical activity, and adherence to preventive medication in patients with minor stroke and transient ischemic attack, and
- 2) to test the effect of that intervention on blood pressure and other cardiovascular risk factors in patients with minor stroke and transient ischemic attack.

3.3 Hypothesis

The hypothesis of the study is that early client-centred patient counselling with repeated follow-up sessions after discharge can reduce the blood pressure through smoking cessation, physical activity, and improved adherence to preventive medication in patients with minor stroke and transient ischemic attacks compared to simple encouragement to lifestyle change.

4 Populations

4.1 Study unit

The study unit will be individual patients.

4.2 Target population

The target population is hospitalized patients with recent minor stroke or transient ischemic attack, who are discharged to their own home, with only minor neurological deficits and do not require specialized rehabilitation.

4.3 Study population

We will include patients with acute minor stroke or TIA admitted to the Department of Neurology at Nordsjællands Hospital (n=40).

Inclusion criteria

- Male or female, age \geq 18 years old
- TIA (ICD-10 G45.9) or stroke (ICD-10 I61, I63, I64) with a Scandinavian Stroke Scale of 45-58.
Diagnosis must be confirmed by a neurologist
- Able to give a valid written consent

Exclusion criteria

- Severe barriers to communication
- Not able to use a telephone
- Severe disability prior to the stroke (WHO Performance Status >2; mobilised less than 50 % of the day)
- Active abuse of alcohol or narcotics
- Severe psychiatric illness (affective disease, dementia, schizophrenia, anxiety)

5 Study design

The study will be a parallel group randomized controlled feasibility trial. Participants will be randomly allocated to either usual care or a counselling intervention, with follow-up sessions post-discharge with 3-4 weeks intervals in 12 weeks.

Intervention

Participants in the intervention group will receive targeted counselling in lifestyle changes focusing on smoking cessation, everyday physical activity, and adherence to preventive medication. The primary aim of the initial counselling session will be to assess the participant's intentions and willingness to change behaviour, and to support the participant in establishing realistic goals. The participants will be encouraged to bring a relative or close friend to the initial counselling session, who can be a support for the participant after the discharge.

Ahead of the initial counselling session we will do a detailed assessment of the participant's lifestyle and physical condition; including an assessment of lung function and oxygen uptake.

After the participants are discharged from the hospital we will do 3-4 follow up counselling sessions. The aim of these sessions will be to re-evaluate the previous goals or to re-assess the participant's willingness to change if the participant continues to be ambivalent about lifestyle changes.

The participant's level of physical activity will be monitored from the discharge to the last follow up after 12 weeks. The participant will be handed out an activity tracker from the hospital which will record all movement day and night.

Usual care

Participants in the control group will receive the standard care, which include a review of prescribed medication, and both verbal and written encouragement of a healthy lifestyle.

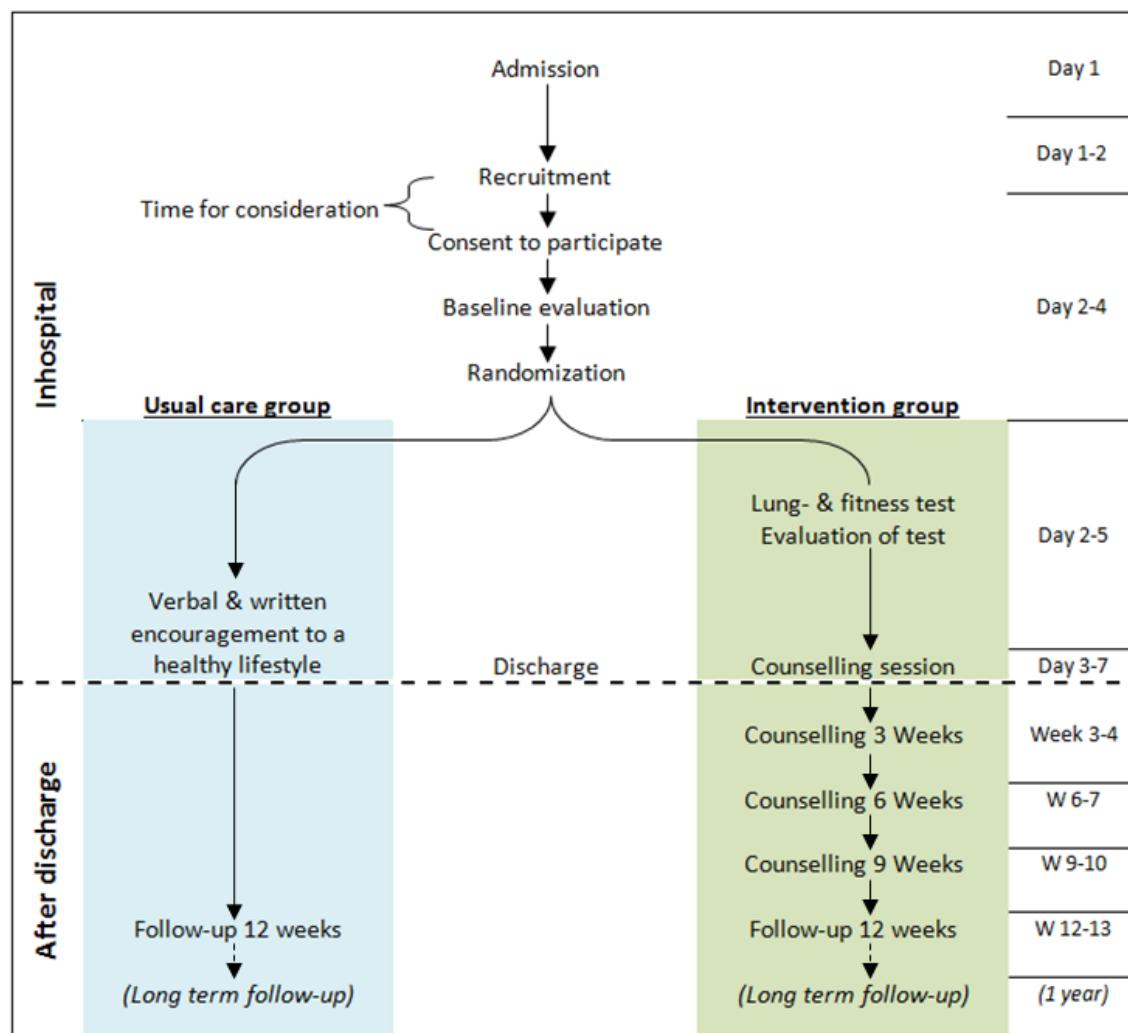


Figure 1 Flowchart of recruitment, inclusion & allocation of participants

6 Recruitment

6.1 Sampling procedure

Potential candidates will be contacted by the investigator while they are in the hospital, usually within the first few days, and asked if they want to participate. Before inclusion a set of control questions are asked to evaluate eligibility and participation is approved by a neurologist.

Potential candidates are informed that participation is voluntary and that consent to participation can be withdrawn at any time. Participation or non-participation will not affect any other parts of the treatment.

6.1.1 Source of study units – Study population

Participants will be recruited from the Department of Neurology at Nordsjællands Hospital.

6.1.2 Inclusion/exclusion criteria for sampling

Patients will be eligible if they have one of the defining diagnoses, as confirmed by a clinical examination by a neurologist, and are adults and able to give a valid written consent.

To make the study more feasible we will have to exclude patients who are not likely to complete the intervention.

Verbal client-centred counselling is a significant part of the intervention and telephone counselling might be part of the follow-up. Therefore, patients will not be able to participate if they have severe communication barriers, such as aphasia, or are unable to use a telephone.

Patients with an active abuse of alcohol or narcotics will not be eligible to participate as they often will need a more intense type of intervention.

Motivation for physical activity is also a central part of the intervention and the participants must be able to be physically active by themselves. Therefore, we will not include patients who prior to the stroke were unable to walk freely or immobile due to other disabilities.

Patients with severe mental illness often have reduced self-efficacy believes and their ability to change lifestyle behaviour can therefore be limited. For these groups of patients a more intensive type of intervention might be needed. This is beyond the scope of this study, but will be treated in another part of the research program.

7 Data management

7.1 Variables

7.1.1 Outcome variables

Measures of feasibility

The primary outcome measure will be the rate of participation in the study; measured as:

- 1) the proportion of patients eligible for the study out of all patients with stroke admitted to the Department of Neurology,
- 2) the proportion of patients accepting to participate in the study, and
- 3) the degree of adherence to the intervention (proportion of attendance in follow-up sessions)

Aside from participation we will evaluate the participants' satisfaction with the overall intervention and single parts of the intervention.

Variable	Measure	Type/scale	Source
Admissions	Number of patients admitted in the study period	Continuous	
Eligibility	Number of patients who would be candidates for participation	Continuous	
Recruitment	Number of participants recruited	Continuous	
Adherence	Number of participants completing the treatment Degree of participation	Continuous	
Satisfaction	Five level Likert Scale	Ordinal	

Secondary outcome

Measure of effect

The secondary outcome measure will be arterial blood pressure measured 12 weeks after the start of the intervention. The arterial blood pressure will be measured as a continuous variable in mmHg. The participant should be sitting still and resting for ten minutes before the measurement. To avoid extreme values the measurement will be repeated three times with a few minutes apart and the median value will be used for the statistical analysis.

This outcome measure was chosen because hypertension is the most significant risk factor for stroke and TIA (5) and because previous studies have found that it might be possible to lower the blood pressure through lifestyle interventions (8).

Tertiary outcomes

Tertiary outcomes after 12 weeks will include:

Variable	Measure	Type/scale	Source
Changes in behavior			
Smoking	Daily; weekly; Rarely; Former; Never smoked	Categorical	B
Physical activity	Questionnaire	Ordinal	B
Adherence to medication	Questionnaire	Continuous	B
Anthropometric measures			
Body weight	Measured (kg)	Continuous	C
Height	Measured (cm)	Continuous	C
Waist + hip circumference	Measured (cm)	Continuous	C
Patient reported outcomes			
Fatigue	Questionnaire		B
Self-rated health	Two item questionnaire	Categorical	B

Secondary outcomes after one year will include:

Variable	Measure	Type/scale	Source
New stroke/TIA	Event + days till event	Categorical/time	A
Cardiac admission	Event + days till event	Categorical/time	A
Death	Event + days till event	Categorical/time	A

7.1.2 Other variables

Baseline data

Before the participants are randomized following baseline data will be collected (*the brackets state the type of data*):

Variable	Measure	Type/scale	Source
Diagnosis	ICD-10; established through clinical exam/CAT scan	Categorical	A
Gender	Male/Female	Categorical	A
Birthdate		Date	A
Symptom onset		Date/time	A/B
Admission		Date/time	A
Living arrangement	Living alone; living with partner; care facility; other	Categorical	B
Performance status (prior)	WHO performance status	Ordinal	B
Self-rated health	Two item questionnaire	Ordinal	B
Alcohol consumption (/week)	Within/above recommended level (7/14 units/week)	Categorical	B
Smoking	Daily; weekly; Rarely; Former; Never smoked <i>For current smokers the amount and type of tobacco is also recorded</i>	Categorical	B
Physical activity		Ordinal	B
Comorbidities	Charlson's Comorbidity Index: Aggregated scale based on weighted scores of presence or non-presence different diseases Individual diseases or groups will be coded as Y/N and the CCI will be calculated from these	Ordinal	A/B
Body weight	Measured (kg)	Continuous	C
Height	Measured (cm)	Continuous	C
Waist + hip circumference	Measured (cm)	Continuous	C
Stroke severity	Scandinavian Stroke Scale; Sub-scores: Consciousness, eye palsy, arm palsy, hand palsy, leg palsy, orientation, speech (dysphasia), facial palsy, gait	Ordinal	C
Vital signs	Early Warning Score; Sub-scores: Respiration rate, oxygen saturation, heart rate, temperature, systolic/diastolic blood pressure, consciousness	Ordinal	C
Cardiac rhythm	ECG: Normal; arterial fibrillation; other arrhythmia	Categorical	C
Blood glucose	S-glucose at admission; HbA1c	Continuous	C
Blood lipids	Total cholesterol, LDL, VLDL, HDL, triglycerides	Continuous	C

7.2 Data collection

All data will be collected by one of the study investigators using electronic case report forms (eCRF) on the RedCap platform. Only consent forms will be on paper.

The sources of data will be either:

- A) Electronic medical records. At this point it is not technically possible to transfer data from the electronic medical records and the data therefore to be entered manually using the eCRF,
- B) Structured interviews with the patients (and relatives if allowed) using standardized questions,
- C) Clinical or para-clinical examinations of the patient

7.3 Database construction and handling

Identifiable data (Names and CPR numbers) will be kept separate from any sensitive data. It will be kept in a key file on another data drive on another server than any other data.

Electronic data will be stored on a Region Hovedstaden server with automatic access logging and data back-up. Access to the data will be password protected using Region Hovedstaden user id (BAM ID).

All paper forms (*consent forms*) will be stored in a locked cabinet in the Department of Neurology at Nordsjællands Hospital.

7.4 Data control and editing

To avoid extreme values the eCRF will have set ranges of plausible values for numerical variables and it will not be possible to enter values outside the ranges.

Before data analysis the data will be checked for missing values. If values are missing we will attempt to reconstruct the information from medical records or by contacting the participant.

The data will be tested for abnormal values by the primary investigator:

Dates – The dates of symptom onset, admission, and discharge will be compared to ensure the differences are not unrealistically bigger than expected, and by testing if any dates are outside the study period.

Categorical variables – Will be checked for missing or illegal values with frequency distributions

Numerical variables – Will be checked for extreme/illegal values with summary statistics and by histograms/boxplots

7.5 Data processing for statistical analysis

The primary outcome measure is systolic blood pressure, which is rarely normally distributed. To make it normally distributed before analysis it should probably be transformed using the natural logarithm.

8 Statistical analysis

8.1 Sample size calculations

The study in the current form is a randomized feasibility study where the main objective is to test if the intervention and study design is feasible enough for a full size study randomized controlled trial. We will therefore only include 40 participants in this phase of the study.

A full size randomized controlled trial will no doubt require a larger sample size if we were to expect an effect to be found. In a meta-analysis of fairly similar interventional studies Lawrence et al. found that the weighted means of the systolic blood pressure were 132.5 (SD 18.3; n=682) mmHg in the intervention groups and 136.2 (SD 21.5; n=725) in the control groups, respectively, and with a mean difference of 4.21 mmHg (95%CI 2.18-6.24).

Using the estimates from Lawrence et al. we can estimate the sample size needed with the method for comparing two means as reported by Kirkwood & Stern ((12)p 420) with the following assumptions:

- An equal number of participants are allocated to the two groups
- The blood pressure values are approximately normally distributed
- An alpha of 5 percent (probability of Type I error) and a beta of 20 percent (probability of Type II error)

From this it is estimated that we will need a sample-size of 596 (298 in each group), not adjusting for losses to follow-up.

8.2 Descriptive analysis

The recruitment, randomization, allocation, and follow-up will be described in a flow-chart stating how many participants were available at each step. We will report characteristics of patients, who are either: excluded, non-consenting, or lost to follow-up in as much detail as possible.

To ensure the external validity of the study we will thoroughly report the characteristics of the participants, both collectively and by treatment group. Participant characteristics will be reported in a table with columns for both treatment groups and a p-value for the differences between treatment groups. The p-values will be calculated using student's test for continuous variables and chi-squared test or fisher's exact test for categorical variables.

8.3 Statistical analysis

Hypothesis testing for the secondary outcome (systolic blood pressure) will be done as intention-to-treat (including all participants allocated) using a paired t-test comparing baseline systolic blood pressure with systolic blood pressure measured after 12 weeks. Results will be reported as mean difference of changes with 95 percent confidence intervals.

Tertiary outcome measures will be analyzed as intention-to-treat using unpaired student t-test for continuous variables and either chi-squared test or fisher's exact test for categorical variables. Treatment allocation will be blinded to the investigator.

Statistical analyses will be done in R 3.3.1/R Studio 0.99. A significance level of 5 percent will be considered statistically significant.

9 Validity and bias

9.1 Data sources

Administrative information (e.g. time of admission/discharge) is recorded real-time and is therefore reasonably reliable. Medical information (e.g. comorbidities) should be confirmed by clinical or para-clinical tests if possible. All information obtained from the medical records will be verified with the participant to sort out flawed information.

The validity of information obtained from participant interviews can be affected in different ways. There might be problems with the internal validity of the questions used, which means that the

answers that are given might not represent what we think they are. Also participants might not be completely honest in their answers and we do not always have ways to validate them.

The biggest threat to the validity of the study will be missing data; especially due to participants been lost to follow-up. Participants will not always be missing at random. They might have some commonality, which will result in an uneven representation.

9.2 Selection bias

In the study we wish to estimate the feasibility and effect in patients who would receive the treatment in clinical practice. One of the criteria for inclusion in the study is the willingness to participate. Most likely some patients will decline the invitation to participate. There could therefore be a potential selection bias, which could result in a skewed estimation of the effect.

9.3 Confounding variables

In theory the random allocation of treatment should eliminate the effect of other confounders, as they would be equally distributed in the two groups. But given the limited sample-size we cannot be certain that this will be the case. One strategy to avoid this could be to stratify the randomization be a likely confounder (e.g. hypertension or smoking). But at this point we are not sure which confounder would be the best to stratify by and this will therefore be part of the feasibility evaluation.

9.4 Other biases

Ideally both participants and investigators should be blinded as much as possible in clinical trials to avoid confirmation bias. In this study it will not be possible to blind the participants to the treatment group, as they are part of the intervention.

It would be a possibility to blind the assessor who conducts the follow-up measurements. But we cannot be sure that the assessor remains blinded, as the participant might reveal the allocation.

10 Limitations of the study

The study will have several limitations.

Although a randomized controlled trail is optimal for testing treatment effects, this study design also has some disadvantages. Because we select eligible patients to be included in the study we will also introduce a selection bias. To make the study more feasible with a small sample size we will have to exclude patients who are likely not going to complete the intervention or who have needs beyond what we treat in our setting, e.g. patients with addictions. This will of course reduce the generalizability of the study.

This also means that we cannot use data from this study to estimate the prevalence of lifestyle- and behavioural factors in the target population. The prevalence of such factors will be important in estimating how big an effect of the intervention we could expect in the target population. If we wanted to estimate the prevalence we would need a representative sample of the population.

Patients with other types of neurological diseases could potentially benefit from similar lifestyle and behavioural interventions. Part of the purpose of the study is to establish a treatment option for patients with minor stroke and transient ischemic attacks who are discharged to their own home, because treatment options for this patient group is limited at the moment. If we can establish a feasible

and effective treatment for this patient group the next step would be to test the feasibility and effect in other types of patients.

To estimate the effect of a treatment we have to compare it to something else. As there is already an established patient pathway for patients with stroke we can only compare the new treatment to the 'usual care' to see if it is superior to this. The disadvantage of this is that the usual care can vary between hospitals and countries. This can influence the transferability of the results from the study setting to other clinical settings.

11 Ethical considerations

The study will be conducted in accordance with the Helsinki-declaration (13); including respect for the participants' autonomy and right to informed consent. The participants will be informed that the participation in the study as a whole and the single parts of it will be voluntary and that they have the right to decline participation at any time and without giving a cause for their refusal.

The inconveniences of participating will be minor and we are convinced that the potential benefits will outweigh the drawbacks. The main inconveniences of the study will be withdrawing symptoms, associated with smoking cessation, and muscle soreness from increased physical activity. Generally this will be both minor and transient.

The use of a control group as a comparison is necessary if we wish to find evidence of the hypothesised effect of the treatment and gain a better understanding of the variation in the outcome measures. It will also be necessary to test the feasibility of the randomization process prior to the design of a full scale randomized controlled trial. The treatment of the participants in the control group will at no point be inferior to the treatment of non-participants.

11.1 Project approval

The study has been reviewed by the Regional Scientific Ethics Comity (H-17040484). They ruled that this type of intervention did not require an ethics committee approval.

The gathering, storage, and handling of sensitive personal data will require consent from the study participants and an approval from the Danish Data Protection Agency.

11.1.1 Confidentiality and anonymity

All sensitive and identifiable data will be kept confidential in accordance with the guidelines from the Danish Data Protection Agency. Doing the project period the data will be semi-anonymized (personal identifiers, e.g. names and CPR numbers, are kept separate from all other data). When the study is finished the data will be anonymized by deleting all identifiable data.

11.2 Authorship and publication rights

Results of the study will be published in peer-review scientific journals as early as possible. Results will be published regardless of them being positive, negative, or inconclusive.

The principal investigator (JML) will make the first draft of all publications under the supervision of the other members of the project group. The order of authorship will be in order of contribution and has been agreed upon in the project group beforehand. The rights and responsibilities of the authors will be in accordance with the *The Danish Code of Conduct for Research Integrity* (14).

12 Project management

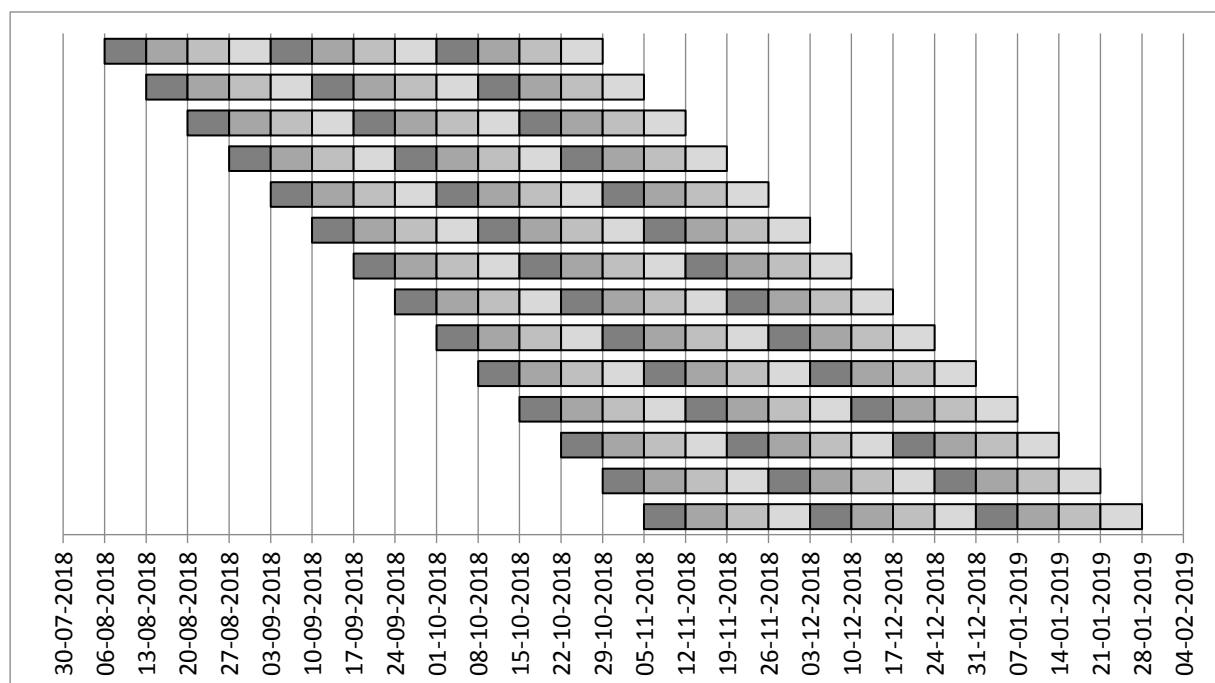
12.1 Project group

The execution of the project will mainly be managed by Jacob Liljehult (RN) under supervision of Thomas Christensen (MD).

The whole project group will participate in the design of the study and the analysis, evaluation, and interpretation of the study results.

13 Timeline and milestones

If three participants are recruited per week the desired number of participants could be included over a 14 week period. With the follow-up period of 12 weeks it will then take 25 weeks from the first participant is included to the last participant is finished.



13.1 Project organization

The project was initiated as part of the *CIRE neuro/psyk* research program in collaboration between Nordsjællands Hospital, Hillerød; The Metropolitan University College, Copenhagen; and The University Hospitals Centre for Health Research UCSF, Copenhagen University Hospital (Rigshospitalet).

The instigators of the *CIRE neuro/psyk* research program consist of researchers and managers from UCSF and Metropolitan University College, in collaboration with the UCSF steering committee consisting of representatives of the hospital managers in Region Hovedstaden.

13.2 Budget

The three organizations will all contribute with a share of 500,000 kr. intended for salaries. Other expenses will be covered though public or private funding.

Items	Note	Year			Total	Reserve Internal funding	Reserve External funding	Deficiency
		1. y 2017-18	2. y 2018-19	3. y 2019-20				
VIP-salary:		kr.	kr.	kr.	kr.	kr.	kr.	kr.
ph.d.-fellow		527.420	527.420	527.420	1.582.260	1.000.000		582.260
TAP-salary:								
Equipment:								
Equipment		75.000			75.000		25.000	50.000
Installation/service								
Spending								
Licences		10.000	10.000	10.000	30.000			30.000
Running expenses:								
Facilities	(NOH)							
Provisions								
Transportation								
Storage								
Other:								
Conferences			5.000	5.000	10.000			10.000
Travelling			12.000	12.000	24.000			24.000
Fees (publications)		15.000	15.000	15.000	45.000			45.000
Training, meetings								
Monitoring								
Statistical assistance	(NOH)							
Proof reading								
Achieving								
Overhead								
Tuition fee	(NOH)	50.000	50.000	50.000	150.000	150.000		
Total		677.420	619.420	619.420	1.916.260	1.150.000	25.000	741.260

14 Deliverables – Reporting and dissemination

Results of the study will be published in international peer-reviewed scientific journals and presented on national and international conferences. Results will be made public regardless of them being positive, negative, or inconclusive.

15 References

1. Feigin VL, Forouzanfar MH, Krishnamurthi R, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2014;383(9913):245-254.
2. Ingeman A(). Dansk Apopleksiregister - Årsrapport 2013. DAR 2014;10.
3. Skyhøj Olsen T. Chapter 21 Stroke recurrence and prognosis after stroke. *Handbook of clinical neurology*, 3rd ser., v. 92; *Handbook of clinical neurology*, v. 92 Edinburgh; New York: Elsevier; 2008. p. 407-421.
4. Hankey GJ, Jamrozik K, Broadhurst RJ, et al. Long-term disability after first-ever stroke and related prognostic factors in the Perth Community Stroke Study, 1989-1990. *Stroke* 2002;33(4):1034-1040.
5. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet* 2010;376(9735):112-123.
6. Dansk selskab for apopleksi. Referenceprogram for behandling af patienter med apopleksi. 3.th udg. København: Dansk selskab for apopleksi; 2012.
7. Wessol JL, Russell CL, Cheng AL. A Systematic Review of Randomized Controlled Trials of Medication Adherence Interventions in Adult Stroke Survivors. *J Neurosci Nurs* 2017;49(2):120-133.
8. Are multimodal stroke secondary prevention interventions effective and how are they 'received' by patients and their families? *International Journal of Stroke*. Conference: UK Stroke Forum 2015 Conference. Liverpool United Kingdom. Conference Publication: (var.pagings). 10 (pp 27); SAGE Publications Inc.; 2015.
9. Deijle IA, Van Schaik SM, Van Wegen EEH, et al. Lifestyle Interventions to Prevent Cardiovascular Events After Stroke and Transient Ischemic Attack: Systematic Review and Meta-Analysis. *Stroke* (00392499) 2017;48(1):174.
10. Lager KE, Mistri AK, Khunti K, et al. Interventions for improving modifiable risk factor control in the secondary prevention of stroke. *Cochrane Database Syst Rev* 2014;(5):CD009103. doi(5):CD009103.
11. Moller T, Lillelund C, Andersen C, et al. At cancer diagnosis: a 'window of opportunity' for behavioural change towards physical activity. A randomised feasibility study in patients with colon and breast cancer. *BMJ Open* 2013;3(11):e003556-2013-003556.
12. Kirkwood BR, Sterne JAC, Kirkwood BR. *Essential medical statistics*. 2nd udg. Malden, Mass.: Blackwell Science; 2003.
13. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310(20):2191-2194.
14. Uddannelses- og Forskningsministeriet. Danish code of conduct for research integrity. Kbh.: Ministry of Higher Education and Science; 2014.