

BMJ Open Multimodal individualised intervention to prevent functional decline after stroke: protocol of a randomised controlled trial on long-term follow-up after stroke (LAST-long)

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ABSTRACT

Introduction Multimodal interventions have emerged as new approaches to provide more targeted intervention to reduce functional decline after stroke. Still, the evidence is contradictory. The main objective of the Life After Stroke (LAST)-long trial is to investigate if monthly meetings with a stroke coordinator who offers a multimodal approach to long-term follow-up can prevent functional decline after stroke.

Methods and analysis LAST-long is a pragmatic single-blinded, parallel-group randomised controlled trial recruiting participants living in six different municipalities, admitted to four hospitals in Norway. The patients are screened for inclusion and recruited into the trial 3 months after stroke. A total of 300 patients fulfilling the inclusion criteria will be randomised to an intervention group receiving monthly follow-up by a community-based stroke coordinator who identifies the participants' individual risk profile and sets up an action plan based on individual goals, or to a control group receiving standard care. All participants undergo blinded assessments at 6-month, 12-month and 18-month follow-up. Modified Rankin Scale at 18 months is primary outcome. Secondary outcomes are results of blood tests, blood pressure, adherence to secondary prophylaxis, measures of activities of daily living, cognitive function, physical function, physical activity, patient reported outcome measures, caregiver's burden, the use and costs of health services, safety measures and measures of adherence to the intervention. Mixed models will be used to evaluate differences between the intervention and control group for all endpoints across the four time points, with treatment group, time as categorical covariates and their interaction as fixed effects, and patient as random effect.

Ethics and dissemination This trial was approved by the Regional Committee of Medical and Health Research Ethics, REC no. 2018/1809. The main results will be published in international peer-reviewed open access scientific journals and to policy-makers and end users in relevant channels.

Trial registration number ClinicalTrials.gov Identifier: NCT03859063, registered on 1 March 2019.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The randomised controlled trial with blinded assessments, aiming to investigate if a multimodal intervention for 18 months after stroke can prevent functional decline, is unique.
- ⇒ The complex intervention close to the real world makes this a pragmatic trial, which also is a strength.
- ⇒ Another strength is the examination of long-term results within the primary care.
- ⇒ A potential threat to the study design is the risk of contamination of the intervention to the control group.
- ⇒ Despite broad inclusion criteria, there is also a risk of selection bias, that is, the healthiest patients are most motivated to participate.

INTRODUCTION

Stroke is the third leading contributor to disability-adjusted life years worldwide.¹ Due to the ageing population and decreasing stroke mortality, the absolute number of stroke survivors is increasing.² Most patients experience significant improvement in function during the first weeks and months after stroke.³ However, a large proportion of those still alive 5 years after onset of symptoms are dependent and in need of healthcare services.⁴⁻⁶

Depending on age and stroke severity, 10%–50% develop dementia within the first year after stroke.^{7 8} Size and location of the stroke, prestroke resilience and comorbidity, acceleration of degenerative processes triggered by the stroke itself or by physiological disturbances such as delirium and systemic disorders in the acute phase are among various factors probably contributing to early decline in function, while decline in the long term could be related to frailty, inadequate

rehabilitation, recurrent stroke, cardiovascular health and neurodegeneration.^{9–12}

Secondary prevention with focus on optimal medication and advises on lifestyle changes is an important part of evidence-based stroke treatment. Regular use of anti-thrombotic treatment (cerebral infarction), antihypertensive treatment, statin therapy and glycaemic control are recommended to prevent recurrent stroke. Patients are also advised to stop smoking, limit their alcohol consumption, comply with a healthy balanced diet and set healthy weight loss goals for those who are overweighted.^{13 14} Furthermore, routine activities should be supplemented by moderate physical exercise 4–7 days per week to accumulate 150 min per week.^{14–16}

Even though it is shown that optimal secondary prevention is associated with up to 80% reduction in the risk of early recurrent vascular events after transient ischemic attack (TIA) or stroke,¹⁷ it is well known that there is substantial variation in adherence to the recommendations given by the guidelines.^{18 19} Some studies have shown that half of the participants stopped taking their prescribed drugs 1 year after the stroke,²⁰ and activity levels are shown to be far below the recommendations.²¹ Different approaches to increase adherence have been tested in clinical trials, showing that motivational interviewing could improve adherence to pharmacological treatment,^{22 23} and tailored counselling might improve participation in physical activity after stroke.²³ In the Life After Stroke (LAST) study, we showed that stroke survivors receiving regular individualised coaching on physical activity and exercise were more active than participants receiving standard care.^{24 25}

It is also a challenge that a large proportion of the patients who had a stroke are elderly with comorbidities suffering from functional decline and frailty even before their stroke.²⁶ The huge variation in symptoms and rate of decline suggest a need to better identify the risk profiles and to provide targeted interventions to reduce functional decline after stroke. In addition, patient organisations are asking for better coordination and access to available services. Hence, multimodal interventions have emerged as new approaches for follow-up. These models aim to ensure that multiple aspects of secondary prevention are being considered and coordinated. Two recent studies^{27 28} showed no beneficial effect of a multimodal intervention that was given during a period of 12 and 24 months, respectively, while the Integrated Care for the Reduction of Secondary Stroke model²⁹ showed to be superior to standard care with respect to risk-factor management. It is important to notice that adherence to the multimodal interventions also is challenging.²⁷

Due to insufficient evidence, the effect of follow-up by a dedicated stroke coordinator within the primary healthcare system who will apply a multimodal approach to identify the risk profile and set up a goal directed treatment plan according to individual needs should be investigated.

Objectives

The main objective of the LAST-long trial is to investigate the benefit of regular meetings with a stroke coordinator for 18 months. In collaboration, the patient who had a stroke and coordinator will identify the individual risk profile, agree on individual goals and set up a treatment plan aiming to prevent functional decline in the long term after stroke.

The following hypothesis will be tested:

1. A long-term multimodal individualised treatment programme is superior to standard care;
 - In preventing functional decline.
 - In controlling risk factors such as, blood pressure, low-density lipoprotein (LDL) and glycated haemoglobin (HbA1c).
 - In preventing recurrent stroke and other vascular events.
 - In improving self-perceived health, after stroke.
2. A long-term multimodal individualised treatment programme is more cost-effective than standard care after stroke.

METHODS

Study design

LAST-long is a pragmatic single-blinded, parallel-group randomised controlled trial performed at 4 centres in Norway; 2 university hospitals and 2 local hospitals, in close collaboration with the primary healthcare service in 6 municipalities of 45 000–200 000 inhabitants.

In LAST-long, patients are being screened for inclusion and recruited into the trial at the out-patient clinics 3 months post stroke. Furthermore, there are follow-up assessments at each hospital at 6, 12 and 18 months after inclusion. The study design is displayed in [figure 1](#).

Participants

The majority of the Norwegian stroke population suffers from mild-to-moderate stroke.³⁰ We regard this part of the population to be the most suitable for preventing functional decline. Hence, patients fulfilling the following criteria are being considered for inclusion:

- ▶ Diagnosis of first ever or recurrent stroke (ischaemic stroke or haemorrhage).
- ▶ Available for inclusion 2–4 months after stroke.
- ▶ Aged ≥18 years.
- ▶ Resident in one of the participating municipalities.
- ▶ Modified Rankin Scale (mRS) <5.
- ▶ Able to understand the Norwegian language.
- ▶ Able and willing to sign informed consent (see online supplemental file 1).
- ▶ To target patients at increased risk of functional decline at least one of the following inclusion criteria must be met:
 - Less than 10 points on Short Physical Performance Battery (SPPB).
 - Less than 26 points on Montreal Cognitive Assessment (MoCA).

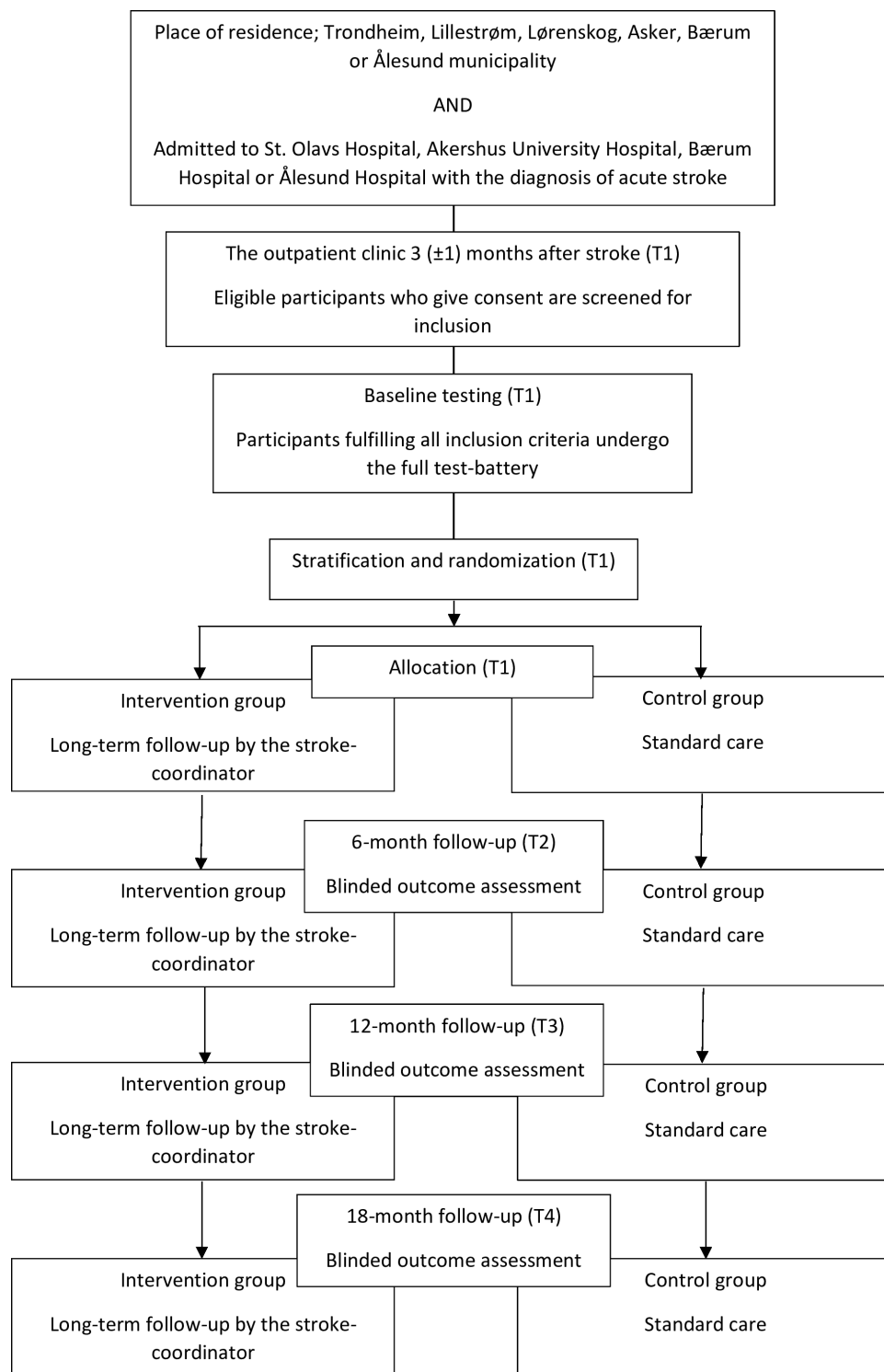


Figure 1 Study design.

More than 27 points on the 7-item version of the Fatigue Severity Scale (FSS-7).
 More than 7 points on the anxiety items on Hospital Anxiety and depression Scale (HADS).
 More than 7 points on the depression items of HADS.
 Not able to draw 10 horizontal lines within 20s (item 3 on Advanced Hand Activities, Motor Assessment Scale).

Exclusion criteria:

- ▶ Life expectancy < 12 months.
- ▶ Other serious diseases judged by the physician to make it difficult to comply with the intervention (ie, serious neurological diseases, dementia or drug abuse).
- ▶ Already included in another intervention study.

Recruitment and randomisation

Patients receive written information about LAST-long along with the notice for the compulsory follow-up



assessment at the outpatient clinic 3 months after the stroke. The initial screening is done by the physician at the outpatient clinic who obtains informed consent and screens for exclusion criteria. If the participant is potentially eligible, further screening is subsequently done by the research assistant. If the participant passes all screening tests, they will continue to the full test battery either on the same day or within the next week. Subsequently, randomisation is performed by a web-based randomisation system developed and administered by the Clinical Research Unit, Faculty of Medicine and Health Science, Norwegian University of Science and Technology. Participants are stratified according to age (>80 years), dependency level (mRS<3) and hospital site. They are randomly assigned (1:1), in blocks of varying and unknown size, to the intervention group or the control group.

When the group allocation has been revealed by the computer system, the research assistant informs the participant about the further process. For participants allocated to the intervention group, the research assistant will notify the stroke coordinator and transfer the participant's contact information.

Blinding

This is a single-blinded study. It is not possible to blind patients for the intervention; however, the outcome assessors at 6-month, 12-month and 18-month follow-up are blinded to group allocation. The participants are also emphasised to not revealed their group allocation during the follow-up assessments.

Study setting

The Norwegian healthcare system

LAST-long is performed within the context of the Norwegian public health service that covers all levels of hospital services, rehabilitation and primary healthcare including general practitioners (GPs), physiotherapists, home care services and nursing homes. The healthcare in Norway is organised through four regional health authorities. These provide most hospital services and reimburse rehabilitation service to inhabitants within their respective region. GPs and physiotherapists (outside hospitals) are partly reimbursed by governmental means. Otherwise, each municipality funds, organises and manages all primary health service such as community-based rehabilitation, home-based care and nursing homes.

Interventions

Participants randomised to the control arm will receive standard care only, while participants randomised to the intervention arm will receive the long-term follow-up programme by a stroke coordinator in addition to standard care.

Standard care

All participants in LAST-long undergo evidence-based comprehensive stroke unit treatment in the acute phase and further rehabilitation according to individual needs

after discharge from hospital.¹² The rehabilitation usually consists of inpatient rehabilitation, rehabilitation in the patient's home or at an outpatient clinic and is often limited to the first 3 months for patients with mild-to-moderate strokes but can last for up to 6 months for patients with the most severe strokes and for selected patients even longer. According to the National guidelines, patients are offered a follow-up consultation at the stroke units' outpatient clinic 3 months after stroke.¹³

In Norway, all residents are entitled to a GP. The GP, in collaboration with the primary healthcare service, plays a key role in follow-up of patients who are discharged home after stroke.¹³ It is acknowledged that due to differences in GPs' knowledge, commitment and their heavy workload, there is a considerable variation as to how much follow-up the patients receive. To some degree, the long-term follow-up is dependent on the patients' demand for further treatment.

Long-term follow-up by a stroke coordinator

After 3 months of standard care, patients randomised to the long-term follow-up programme receive follow-up by a new, established community-based stroke coordinator within their municipality. The main role of the coordinator is twofold: (1) to set up an individualised treatment plan and (2) to coordinate access to the existing services. Further details of the intervention are given below:

A study-specific check list (the LAST-long checklist) has been developed based on the World Stroke Organisation (WSO) Post-Stroke Checklist³¹ and Comprehensive Geriatric Assessment (CGA).³² CGA is a technique for multidimensional assessment of frail elderly people, linked with an overall plan for treatment and follow-up, which is shown to be effective for improving survival and function in older persons.^{33 34} The original CGA includes four domains of assessment that are: medical assessment, assessment of function, psychological assessment and social assessment.³² Hence, CGA might also be a useful tool in risk management after stroke. On the other hand, the WSO Post Stroke Checklist, addressing 11 areas, is also aiming to improve long-term stroke care.³¹ In the LAST-long checklist, we have merged the domains from the WSO Post Stroke Checklist and the CGA to cover all relevant areas for long-term follow-up after stroke.

The LAST-long checklist is being used as a guide for a structured interview in order to assess the patients' risk profile within the following domains: (1) physical health and lifestyle factors, (2) mobility and activities of daily living (ADL) function, (3) cognitive function and (4) social function. The domains of the LAST-long checklist are shown in [table 1](#), while more details about the checklist are described in [table 1](#) and in the online supplemental table 1. In addition, a comprehensive instruction guide on how to assess each subdomain in the checklist has been developed. The instruction guide does also include the treatment goals we are aiming for within the different domains. These goals are based on

Table 1 The domains and subdomains of the LAST-long checklist

1. Health and lifestyle	2. Physical function	3. Cognition and mood	4. Social function
1.1. Physical activity	2.1. Activities of daily living	3.1. Cognition	4.1. Living conditions
1.2. Medication	2.2. Mobility, balance and risk of falling	3.2. Communication	4.2. Family
1.3. Smoking, alcohol and drugs	2.3. Vision and hearing	3.3. Fatigue	4.3. Caregivers
1.4. Nutrition	2.4. Bladder and bowel function	3.4. Mood	4.4. Work related matters
1.5. Pain			4.5. Any other matters
1.6. Spasticity			
1.7. Comorbidities			

LAST, Life After Stroke.

recommended guidelines such as the Norwegian national guidelines¹³ and the Europeans Stroke Organisations' guidelines.³⁵

For patients at risk within one or more domains, the stroke coordinator and the participant will agree on an appropriate treatment plan, based on individual goals, aiming to maintain or improve function. The plan will consist of 2–3 achievable goals and corresponding treatment plan. The treatment plan will only make use of already available community-based or hospital-based services as recommended by the stroke coordinator. For example, patients with an increased risk of falling might have as an individual goal to improve balance, and the action point might be to be referred to community-based groups focusing on balance training. The stroke coordinator will then assist in getting access to the balance group.

In the follow-up meetings, the goals and treatment plan will be evaluated, and the coordinator and participant will agree on a new plan for the next month.

The stroke coordinators who are also working as healthcare providers (physiotherapist, occupational therapist or nurse) in the primary healthcare system know the available services in their municipality very well. They collaborate closely with the service office, which makes the decision to access the necessary services. Furthermore, the stroke coordinators are certified in motivational interviewing as a technique to facilitate life-style changes and improve adherence to the treatment plan.

Regular workshops are being arranged for the stroke coordinators to improve adherence to the intervention protocol.

Participants are referred to the stroke coordinator within 2 weeks after inclusion. The follow-up consists of 18 monthly meetings between the participant and the stroke coordinator. Most meetings will be face to face; however, it is allowed for up to 50% online meetings.

A schedule of the first four meetings is illustrated in figure 2.

Data acquisition

The sources of data and time of assessments are listed in table 2, while more details about all variables are described in this section.

Demographics, stroke characteristics, comorbidity and life-style factors

Age, gender, marital status, premorbid living arrangements, working situation and education at time of stroke are obtained as background variables.

Strokes are defined according to the WHO definition³⁶ and classified according to location, subtypes (ischaemic/haemorrhage), imaging markers (CT and MRI) and the TOAST classification.³⁷ Stroke severity is measured by the National Institutes of Health Stroke Scale.³⁸ Treatment with thrombolysis (yes/no) and the use of medications are also registered.

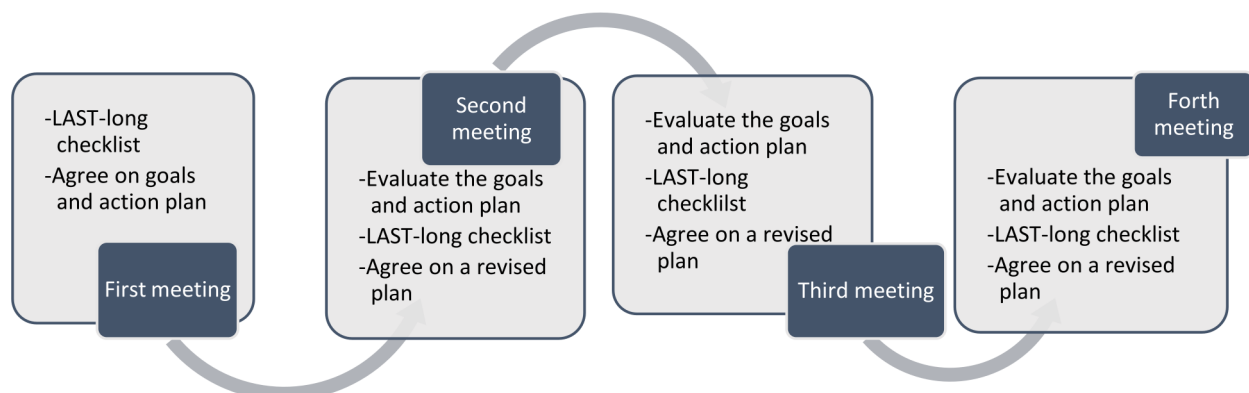


Figure 2 A schedule of the first 4 monthly meetings of the long-term follow-up by the stroke coordinator. These will be continued for 18 months. Motivational interviewing is being used to define the goals and action plan. LAST, Life After Stroke.

**Table 2** Outcome measures

	Sources of data				Time of assessment				
	Medical records	Examination	Questionnaire/ interview	Proxy	T0	T1	T2	T3	T4
Demographics	x		x		x	x	x	x	x
Stroke characteristics									
TOAST	x				x				
Infarction versus haemorrhage	x				x				
CT/MRI findings	x				x				
NIHSS	x	x			x	x			
Comorbidities	x		x		x	x	x	x	x
Medication	x		x		x	x	x	x	x
Smoking habits			x						
Alcohol intake			x			x	x	x	x
Blood samples	x	x			x	x	x	x	x
Blood pressure	x	x			x	x	x	x	x
Body mass index	x	x			x	x	x	x	x
Fall history	x		x			x	x	x	x
Activities of daily living									
Modified Rankin Scale	x	x	x	x	x	x	x	x	x
Barthel Index	x	x	x			x	x	x	x
NEADL			x			x	x	x	x
Cognitive function									
MoCA		x				x	x	x	x
TMT-A		x				x	x	x	x
TMT-B		x				x	x	x	x
GDS		x	x	x		x	x	x	x
Physical function									
SPPB		x				x	x	x	x
Grip strength		x				x	x	x	x
6MWT		x				x	x	x	x
Physical activity									
HUNT PA-questions			x			x	x	x	x
ActivPal		x				x	x	x	x
Patient reported outcome measures									
EQ-5D-5L			x			x	x	x	x
SIS			x			x	x	x	x
FSS-7									
HADS			x			x	x	x	x
Caregivers' experiences									
CSRI			x			x	x	x	x
Relatives' Stress Scale			x			x	x	x	x

Continued

Table 2 Continued

	Sources of data				Time of assessment				
	Medical records	Examination	Questionnaire/interview	Proxy	T0	T1	T2	T3	T4
CSRI, Client Service Receipt Inventory; EQ-5D-5L, The five-level EuroQol five-dimensional descriptive system; FSS-7, The 7 item version of Fatigue Severity Scale; GDS, Global Deterioration Scale; HADS, Hospital Anxiety and Depression Scale; HUNT PA-questions, The physical activity items from the Nord-Trøndelag Health Study questionnaire; MoCA, Montreal Cognitive Assessment; 6MWT, six minute walk test; NEADL, Nottingham Extended Activity of Daily Living index; NIHSS, National Institutes of Health Stroke Scale; SIS, Stroke Impact Scale; SPPB, Short Physical Performance Battery; T0, index hospital stay; T1, Baseline (3-months after stroke); T2, 6-month follow-up; T3, 12-month follow-up; T4, 18-month follow-up; TMT-A, trail making test part A; TMT-B, trail making test part B; TOAST, Trial of Org 10172 in Acute Stroke Treatment.									

MRS³⁹ is used to obtain information about prestroke function. Previous cardiovascular diseases and other comorbidities that might impact the outcome of this trial are obtained by Charlson Comorbidity Index.⁴⁰ Lifestyle factors (smoking status, alcohol consumption and activity levels), blood pressure and body mass index (BMI) are also registered.

Primary outcome

This trial is aiming to prevent decline in global function. Hence, mRS at 18-month follow-up is the primary outcome.

Secondary outcomes

Blood samples, blood pressure, medications and BMI

Blood tests and blood pressure are applied to measure to which extent the participants are achieving their treatment goals for secondary prevention. Non-fasting blood tests include total cholesterol, LDL, high-density lipoprotein, HbA1c, haemoglobin, creatinine and C reactive protein. The use of drugs is collected by questionnaire and from the Norwegian Prescription Database (drug use by Anatomical Therapeutic Chemical Classification System and prescription).

Blood pressure is obtained by a standard procedure of three repeated measures in a sitting position after a 5 min rest. The average of the two last measures is reported.

The BMI is derived from body weight and body length obtained from standardised and calibrated equipment at each site.

LDL \leq 1.8 mmol/L, HbA1c \leq 53 mmol/L and a blood pressure $<$ 140/90 mm Hg are set as the targets in controlling risk factors.^{13 41}

Activities of daily living

In addition to mRS as a measure of global function, basic ADL is measured by Barthel Index,³⁹ while instrumental ADL is measured by Nottingham Extended ADL Scale.⁴²

Cognitive function

Screening of global cognitive function is performed using the MoCA.⁴³ MoCA evaluates several cognitive domains such as memory, visuospatial abilities, executive function, language, abstraction, attention, subtraction, digits forward and backward

and orientation and is also validated for telephone interview.⁴⁴ Global Deterioration Scale (GDS)⁴⁵ is also used as a measure of global cognition and is scored by the assessor, based on the combination of available information from tests and interviews. GDS makes it possible to have a measure of cognition also in participants who are not able to complete the MoCA Scale.

Executive function is measured using Trail making test A and B.^{46 47}

Physical function

Physical performance is measured by SPPB consisting of three subtasks: 4 m gait speed, balance and chair rise. SPPB is validated as a screening tool to identify people at risk of falling ($<$ 10 points) and is increasingly used as an outcome measure of interventions aiming to reduce sedentary behaviour.⁴⁸ Physical capacity is measured by the six minute walk test using the standard test procedure in a 10 m walkway.⁴⁹ Grip strength, which is shown to be an indicator of frailty,⁵⁰ is measured by using a Jamar handhold dynamometer.⁵¹

Physical activity

Standardised questions from the North-Trøndelag Health study⁵² is used to obtain the amount of self-reported physical activity from before the stroke, while ActivPAL activity monitors are used to quantify time spent sitting/lying, standing and walking for 24 hours during 7 days after inclusion and each follow-up assessment.⁵³ The inertial sensor, which is attached to the front of the unaffected thigh, produces a signal related to thigh inclination and can identify posture (sitting/lying from upright activity). This method is previously shown to be valid in the stroke population.⁵³

At least, 150–300 min of moderate intensity aerobic physical activity is set as the target in controlling risk factors.^{54 55}

Patient reported outcome measures

Patient-reported outcome measures capture a person's perception of their own health through questionnaires. They enable patients to report on their quality of life, daily functioning, symptoms and other aspects of their health and well-being. In this study, the Stroke Impact

Scale (SIS)⁵⁶ and the five-level EuroQol five-dimensional descriptive system (EQ-5D-5L)⁵⁷ are chosen as measures of health-related quality of life, while HADS⁵⁸ is used as a measure of emotional distress and FSS-7⁵⁹ as a measure of poststroke fatigue.

Caregivers' burden

By using part 2 of the Client Service Receipt Inventory,⁶⁰ caregivers' work participation and absenteeism are registered. The 15-item Relatives' Stress Scale⁶¹ is used to measure the burden on the caregivers.

The use of health services

Readmission to hospital, length of stay in hospital, diagnosis, diagnostic-related group (DRG) code, outpatient visits (DRG-code), the use of home-based services, physiotherapy, speech therapy, occupational therapy, inpatient and outpatient rehabilitation and long-term and short-term care in nursing home, number of visits to the GP or private physiotherapy and, information about work participation and absenteeism will be collected from national registries collected by use of the national ID number.

Safety measures

Number of deaths, serious falls leading to contact with the GP or hospital, cardiovascular and cerebrovascular events will be recorded in both groups during follow-up from the relevant registers.

Measures of adherence

Adherence to follow-up by the stroke coordinator is obtained by registering the number of attended meetings and the content of these.

Adherence to the treatment plan is obtained by a five-level adherence rating scale, developed for this specific purpose.

Sample size estimation

The sample size calculation method, most close to the mixed model analysis available in the sample size software NCSS 2020, is Analysis of Covariance (ANCOVA). The calculation was based on data from the LAST study,²⁴ with an estimated mean (SD) deterioration of 0.4 (1.47) points on mRS in the control group, and maintenance of function 0.0 (1.44) points in the intervention group. We estimated the correlation between mRS at baseline and 18 months to be $R=0.445$, giving $R^2=0.20$.

We expect to include 150 participants in each of the two groups. With a significance level of 0.05, this gives a power of 76%. This power estimate is slightly conservative, since we also plan to adjust for the following covariates; age, dependency level, hospital site, gender and a measure of stroke severity, which is expected to give a higher R squared than adjusting for baseline mRS alone, that is, with an R^2 of 0.25, 300 participants will give a power of 79%.

Furthermore, we do expect that about 10% of the participants will have missing data at one or more timepoints. By analysing data using a mixed model,

participants with partly missing data will be included in the analysis with data from the available time points. Hence, the effective reduction in sample size is estimated to 4%. This corresponds to 288 participants (144 per group) with complete data, giving a power of 74% instead of 76%.

Data analysis

Mixed models will be used to evaluate differences between the treatment groups for the primary and secondary endpoints across the four time points, with treatment group and time as categorical covariates and their interaction as fixed effects and patient as random effect. The baseline value of the dependent variable will be handled as recommended by Coffman *et al.*⁶² The model will be adjusted for the variables used in stratified randomisation (age, dependency level and hospital), as well as gender and a measure of stroke severity.

Costs will be calculated from volume of health services and corresponding unit costs. Published unit costs will be applied when available. Intervention costs will be calculated in specific based on a microcosting approach.

Cost-effectiveness will be evaluated by calculating the incremental cost-effectiveness ratio (ICER) that is the difference in mean costs divided by the difference in mean quality adjusted life years (QALYs). We calculate QALYs with an area-under-the-curve approach, with the assumption of piecewise linear change in EQ-5D-5L Index values over time. Missing data will be imputed by multiple imputation when relevant and the uncertainty of the ICER will be assessed by applying bootstrapping techniques.

Data management and monitoring

All data will be collected in a paper case report form (CRF) and subsequently plotted and stored in a web based CRF (WebCRF) designed by the Clinical Research Unit at NTNU (<https://www.klinforsk.no/about>). The paper CRFs will be stored in a locked cabinet in a room with admission control during the data collection period. Data will also be stored in the WebCRF during the data collection period. However, when the data collection is completed, all data will be transferred to a secure server at the Norwegian University of Science and Technology (NTNU). The key to the patients' identity will be stored at a separate server.

In line with the General Data Protection Regulation, a Data Protection Impact Assessment has been performed. Cleaning and quality control of data is performed continuously by monitoring the WebCRF. A data management agreement will be signed for everyone who is going to work with the data.

There are no formal data monitoring committee for this study. However, the study progress and possible adverse events are monitored continuously by members of the project administration.

Patient and public involvement

We are collaborating with two user organisations (Landsforeningen for slagrammede and LHL hjerneslag og afasi) in the LAST-long project. Based on experience with user involvement from previous research, we have decided to organise the collaboration in meetings two times per year. In these meetings, planning and implementation of the project has been discussed and also the dissemination and implementation of the results to ensure that future stroke victims will benefit from the LAST-long results. Other stakeholders such as the primary healthcare sector have been defined as partners in this project. Their perspectives will be ensured through their participation and discussion.

ETHICS AND DISSEMINATION

LAST-long is being conducted in accordance with ethical standards given by the Norwegian National Committee for Medical and Health Research Ethics. This trial is approved by the Regional Committee of Medical and Health Research Ethics (REC), REC no. 2018/1809.

A few amendments have been approved. These are mainly approval of adding new researchers to the project and extending the project by adding two new recruitment sites (Bærum Hospital and Ålesund Hospital) and approval of the updated sample size estimations.

The key between the data and the participants' identity is being stored in a separate place only available for a few key personnel. Only anonymous data will be available for analysis and reporting of results. Hence, the participants confidentially will be ensured.

Inclusion in LAST-long is based on oral and written consent from the participants. By excluding patients not able to consent for themselves, it is also a risk that we will lack evidence for the optimal treatment for patients with the most severe strokes. However, as the intervention requires communication and collaboration between the stroke coordinator and participants, it is not feasible to include those without that ability.

The rigorous evaluation of all participants at inclusion and each follow-up assessment should be regarded as a benefit. If any deviations from normal values according to predefined limits on any of the tests are revealed, the patient is informed about this finding and emphasised to contact their GP for further follow-up. However, the extensive test battery could also be a strain. To reduce this burden, participants are given one or more breaks during the test session. We have also made a reduced version of the test battery indicating which assessments that should be prioritised for patients who are not able to complete the whole test battery. Despite this precaution, we cannot exclude withdrawals due to the burden of the follow-up assessments. Some participants might also want to withdraw because of the cognitive tests that can reveal cognitive impairments which in some cases is related to shame. However, all the trained assessors are experienced in communicating and treating patients who had a stroke and they will contribute to reduce this

risk. After the test battery has been completed, the ActivPAL activity sensor is being attached to the unaffected thigh. Participants are told to remove the sensor if they experience any skin reaction from the plaster covering the sensor. The sensor is recording activity pattern for 24 hours. It is only possible to obtain information about energy consumption, number of steps and time in sitting, lying, or standing position to ensure confidentiality.

All scientific results from this trial will be published in leading international peer-reviewed scientific journals, choosing Open Access journals as the first choice. The findings will also be presented at international scientific conferences to disseminate project results to the scientific community and in other ways contribute to the scientific discussion related to long-term follow-up after stroke. Equally important, project results will be disseminated to end users, professional organisations, the general public, policy-makers and the healthcare sector through flyers and oral presentations when appropriate. We are also aiming to inform the general public, both through established media and social media such as Twitter, Facebook and the blog #NTNUmedicine.

In line with open research, the participants are giving consent to share anonymous data for the purpose of use the LAST-long data in future meta-analysis.

DISCUSSION

The main objective of the LAST-long trial is to investigate the benefit of regular follow-up by a new, established community-based stroke coordinator who sets up a treatment plan to prevent functional decline in the long term after stroke. According to the latest update from the UK Medical Research Council, an intervention might be considered complex because of properties of the intervention itself, 'such as the number of components involved; the range of behaviours targeted; expertise and skills required by those delivering and receiving the intervention; the number of groups, settings, or levels targeted, or the permitted level of flexibility of the intervention or its components'.⁶³ The LAST-long intervention complies with several of these properties. First, the intervention consists of several components such as the use of motivational interviewing technique and checklist in the follow-up meetings. Other components are the use of goal setting and a measure of goal achievement in addition to the action plan and a measure of adherence to this. Second, the multimodal approach targets different behaviours depending on the individual needs. Third, the stroke coordinators delivering the intervention need to have specialised expertise about specific poststroke risk factors and available community-based services. Fourth, the multicentre approach with the intervention delivered within six different municipalities indicates that the setting will differ. It might also differ within some of the municipalities depending on the organisation of the stroke coordinator. Finally, the flexibility of the intervention is also considerable. Even though the protocol



states that at least 50% of the meetings should be face-to-face meetings, the COVID-19 pandemic has required the intervention to be flexible to comply with the national regulations for social distancing during the pandemic and introduced challenges and limitations to the possibilities of setting up an optimal action plan.

The evaluation of a complex intervention should go beyond the evaluation of whether the intervention works or not.⁶³ In addition to the primary and secondary outcomes, subgroup analysis should be carried out to support the research question.⁶³ The evaluation should also take into account how the intervention interacts with the context in which it is implemented, how it contributes to system changes and how the evidence can be used to support decision-making in the real world.⁶³ Furthermore, a process evaluation should be included.⁶⁴ The process evaluation of LAST-long is going on along the trial. This evaluation will give a better understanding of the nature of any impact of the intervention. By use of qualitative research methods, we are investigating barriers and facilitators of the intervention experienced by the stroke survivors, the stroke coordinators and their leaders.

In LAST-long, the mRS has been chosen as the primary outcome.³⁹ mRS is a widely used measure within stroke research and it is also frequently used in clinical practice as a measure of disability. Another advantage is that mRS could be assessed via phone interview, which will reduce the risk of missing data for patient not able to show up for the follow-up assessments. Even though the sensitivity of mRS has been questioned,⁶⁵ it was chosen as the primary measure because a small change on this scale is regarded as clinically significant.⁶⁶ In our power calculation, which was based on results from the LAST study,²⁴ a reduction of 0.4 points on mRS was set as a clinically significant decline. However, if the study turns out to show a neutral effect according to the primary outcome, the results from the secondary outcomes should also be considered as an important part of the evaluation. Especially, the patient reported outcomes are of great interest, and in particular the EQ-5D and the SIS that measures self-reported health within different domains and also contains a rating of overall recovery after the stroke.^{67,68} SIS was also considered to be used as the primary outcome and might have been a more appropriate scale to reflect the intention of the intervention. However, SIS is an extensive and time-consuming scale, which require good cognitive function and was therefore considered not to be appropriate as the primary measure.

In the LAST-long trial patients are stratified according to age (18–80 vs 81–100 years), dependency level (mRS 0–2 vs 3–4) and hospital site. Hence, subgroup analysis will be carried out to investigate if the intervention is more beneficial to participants of older age or those being dependent in daily activities. Such information will be helpful in the implementation of this intervention in the next phase.

To improve the long-term follow-up after stroke is one of the main focuses for stroke survivors and their organisations. Two different user organisations have been

involved in this project from the very beginning and they have requested that the benefit of a stroke coordinator as part of the healthcare service should be evaluated. It has also been of great value to discuss the details of the intervention and the recruitment strategy with the stroke survivors. Furthermore, these organisations will play an important role in disseminating the results to the target group.

LAST-long is also conducted in close collaboration with the primary healthcare system to ensure a successful implementation of the intervention.

Strengths and limitation

The randomised controlled multicentre design with blinded assessment performed by trained assessors is considered as a major strength of this trial. However, a potential threat to the trial is the risk of contamination of the intervention to the control group because the stroke coordinators might tend to apply parts of the intervention to other patients they are treating as primary healthcare providers and some of these patients might happen to be in the control group. To reduce this risk, we strongly emphasise that the stroke coordinators should not get in touch with patients in the control group during the 18 month follow-up period. A cluster randomised design could have reduced such risk, but it was not regarded as feasible to apply clusters within the participating municipalities due to great variation in population and organisation of the healthcare service. Further, repeated examinations (at 6, 12 and 18 months after inclusion) for both study arms are another pitfall, which may promote healthy lifestyle and adherence to medical treatment also in the control group. Another risk is poor adherence to the protocol by the participants and the stroke coordinators. This will possibly reduce the difference between the study intervention and standard care, increasing the chance of neutral results. It is also a risk that the intensity of the intervention is too weak to show that it is effective. Hence, if the main result of LAST-long turns out to be neutral, another future trial should investigate if a more intensive intervention of bi-weekly follow-up meetings would be beneficial.

The risk of selection bias is also a potential threat to the external validity of the LAST-long trial. Because we are aiming to maintain function in the long term, our target population are those with mild to moderate impairments after stroke. According to the inclusion criteria, participants should be community dwelling but have some kind of impairment, that is, impaired hand function, mobility or cognition, or symptoms of anxiety, depression or fatigue. These are common symptoms, leaving the participants at risk of functional decline. Even though our inclusion criteria are quite broad, it is still a risk that the healthiest patients are most motivated to participate. Such selection bias will make the study population less representative to the general stroke population and increase the risk of neutral results.

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