Reducing recurrent stroke: Methodology of the motivational interviewing in stroke (MIST) randomized clinical trial

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Rationale **Recurrent stroke is prevalent in both developed and developing countries, contributing significantly to disability and death. Recurrent stroke rates can be reduced by adequate risk factor management. However, adherence to prescribed medications and lifestyle changes recommended by physicians at discharge after stroke is poor, leading to a large number of preventable recurrent strokes. Using behavior change methods such as Motivational Interviewing early after stroke occurrence has the potential to prevent recurrent stroke.**

Aims and/or hypothesis **The overall aim of the study is to determine the effectiveness of motivational interviewing in improving adherence to medication and lifestyle changes recommended by treating physicians at and after hospital discharge in stroke patients 12 months poststroke to reduce risk factors for recurrent stroke.**

Design **Recruitment of 430 first-ever stroke participants will occur in the Auckland and Waikato regions. Randomization will be to intervention or usual care groups. Participants randomized to intervention will receive four motivational interviews and five follow-up assessments over 12 months. Nonintervention participants will be assessed at the same time points.**

Study outcomes **Primary outcome measures are changes in systolic blood pressure and low-density lipoprotein levels 12 months poststroke. Secondary outcomes include self-reported adherence and barriers to prescribed medications, new cardiovascular events (including stroke), changes in quality of life, and mood.**

Discussion **The results of the motivational interviewing in stroke trial will add to our understanding of whether motivational interviewing may be potentially beneficial in the management of stroke and other diseases where similar lifestyle factors or medication adherence are relevant.**

Key words: adherence, motivational interviewing, recurrent stroke, secondary prevention

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DOI: 10.1111/ijs.12107

Introduction

Strokes recur in 6–25% of people (1–3), usually in the first year (1,4,5). The risk of stroke is highest early after the event (4). By five-years poststroke, the cumulative risk of recurrent stroke is 30–40% (5). Recurrent stroke may lead to greater disability, institutionalization, increased risk of dementia, and a high risk of death (6), and therefore, poorer health and economic outcomes (7).

Management strategies for secondary stroke prevention are well established (2,3,5,7–10), yet remain underutilized (8,11). The landmark INTERSTROKE studies suggest that 10 risk factors are associated with 90% of the risk of first-ever stroke (12). Recurrent strokes are largely preventable using similar strategies to that of primary stroke prevention (13). Several trials have attempted to improve secondary prevention of stroke and coronary heart disease through education of patients and/or caregivers (14,15) and improving access to care (16–20). However, these have not improved management of clinical or behavioral risk factors (14–19,21,22), required complex computer systems (20), or were designed for inpatients only (21,22). In a systematic review, lifestyle modifications were shown to be effective for secondary stroke prevention with improvements seen in both lifestyle behavior changes and physiological outcomes (23). A recent study suggests that long-term adherence to nonspecific prescription pills reduced the risk of subsequent vascular events in persons who had a recent ischemic stroke (24). Although adherence to prescribed medications and/or recommendations to lifestyle changes (such as reducing smoking, increasing physical activity) after first stroke are effective strategies to reduce recurrent stroke, in practice, the implementation of these recommendations is poor (25,26). Targeting adherence may be a key to reducing the incidence of recurrent stroke; therefore, it is both appropriate and timely to conduct trials to assess whether new approaches may

improve patient adherence to evidence-based guidelines for secondary stroke prevention (10,27) after hospital discharge.

Motivational interviewing (MI) is a structured, patient-focused (28–33), and cost-effective (34) intervention that was originally developed for the treatment of people with problem drinking, addictions (35,36), and substance abuse management (32,37–40) but has been increasingly used in other areas of medicine (41,42), including stroke (43–47), traumatic brain injury (48), and cardiovascular disease (49–51). The objective of MI is to help the client to explore their ambivalence towards behavior change, and by resolving this ambivalence, facilitating positive behavior change in the individual (42).

A significant benefit of MI on mood early after stroke over usual stroke care was recently demonstrated in a randomized controlled trial (43). Given the evidence for efficacy and cost effectiveness of MI for behaviour change, this intervention has been identified as a high research priority (41,52). However, the majority of trials have been relatively small and no studies have been carried out specifically to test the effectiveness of MI in reducing risk factors related to recurrent stroke. Therefore, a large randomized clinical trial is needed to provide clarity on how MI applies to recurrent stroke. Given its potential to encourage patients to adhere to medication and lifestyle changes recommended by clinicians, this trial is designed to assess the effectiveness of MI in reducing outcomes related to recurrent stroke.

Objectives

The overall aim of the study is to determine the effectiveness of MI in improving adherence to medication and lifestyle changes recommended by treating physicians at and after hospital discharge in stroke patients 12 months postrandomization.

Methods

Trial design

This is a phase III single-blind randomized controlled trial of participants with first-ever stroke (excluding subarachnoid haemorrhage) followed for 12 months after randomization. Participants are randomized to either the MI intervention group (henceforth referred to as MI) or usual care (UC). Recruitment for the trial commenced on March 1, 2011 with the population-based ARCOS IV Incidence and Outcomes Study (53). Figure 1 is a flowchart of the overall trial design of the MIST study.

Patient population- inclusion and exclusion criteria

All consecutive adult (16 years or older) stroke survivors who had a first-ever stroke and are residents of Auckland or Waikato Region are considered potentially eligible for inclusion in the trial. Stroke is defined according to the World Health Organization definition as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin' (54). A diagnostic review committee comprising four stroke neurologists meet fortnightly to confirm the diagnosis of stroke and classification of all ischemic cases. The committee uses medical history, hospital discharge summaries, clinical and laboratory findings (including vascular and cardiac imaging), or necropsy results when available to inform their decisions. A detailed description of the diagnostic review process is available in the article describing the methodology of the ARCOS IV Incidence and Outcomes Study (53).

The main exclusion criteria are (1) recurrent stroke (excluding clinically silent previous strokes); (2) a diagnosis of subarachnoid haemorrhage; (3) significant impairments precluding participation (e.g. aphasia); (4) inability to give informed consent; (5) another condition likely to impact their participation in the trial (e.g. life-threatening condition other than cardiovascular disease); and (6) expected discharge to hospital/nursing home setting where adherence to lifestyle recommendations and medications is beyond participant control.

Ethical approval and trial registration

The study was given ethical approval by the Northern X Regional Ethics Committee for experiments in human subjects and the Auckland University of Technology Ethics Committee. The trial is registered with the Australian New Zealand Clinical Trial Registry (Trial Registration Number: ACTRN 12610000715077).

Recruitment

Between March 1, 2011 and February 29, 2012, potential participants were recruited for the trial from the main ARCOS IV Incidence and Outcomes study (53). Participants eligible for ARCOS IV were approached for participation in the MIST study during the period of recruitment for ARCOS incidence study. Additional participants were recruited from the Waikato region for the same period. From March 1, 2012, participants will be recruited from all four Auckland public hospitals, and the recruitment period is expected to continue up to December 2013. Daily searches of admissions data are carried out in all four Auckland region public hospitals for records suggestive of a diagnosis of first-ever stroke.

Informed consent

Potentially eligible participants are identified by a hospital-based research assistant (RA) via regular checks of each hospital database for new admissions and participation at weekly medical and diagnostic team meetings for relevant hospital wards/units. Potential participants are approached by an RA to give informed consent to participate. If consent is obtained, baseline case record forms (CRFs) will be completed.

Screening

All participants who meet the main inclusion criteria and provide informed consent undergo a face-to-face detailed screening process with a study RA to ensure that they meet the eligibility criteria for randomization into the trial. Table 1 shows the eligibility screening criteria used to identify participants eligible for randomization. Information from medical records is also used when available to aid the screening process. After completion of eligibility screening, participants identified as meeting the eligibility criteria are randomized.

Randomization

Eligible study participants are randomized to either the MI or UC groups using web-based computerized randomization software. A stratified minimization algorithm is used to randomize participants in order to balance possible prognostic factors [i.e. age (<70,

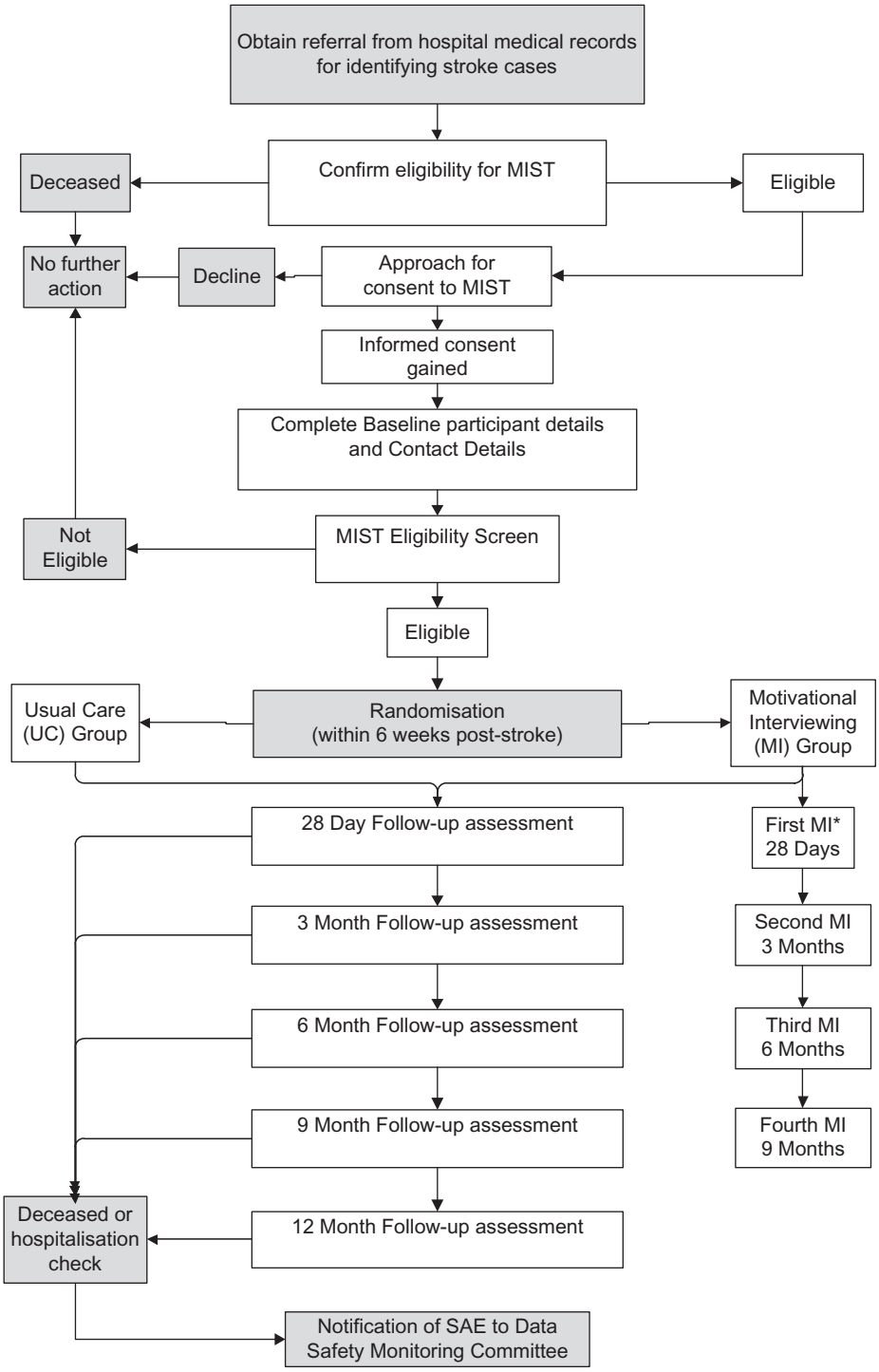

Fig. 1 Flowchart of motivational interviewing in stroke (MIST) study procedures.

70+), stroke severity (Barthel Index <18 and ≥18), gender and race-ethnicity (European, non-European)] across the two groups.

Following randomization, a confirmation letter is sent to the study participant that includes a reminder of the timing of primary outcome measures requested for the purpose of the study (blood pressure and blood lipid cholesterol levels at 12 months after stroke). A reminder letter is also sent to the participant, along with a blood request form for a free blood lipid test, one-month prior to the 12 month assessment date. In addition, a letter is sent to the participant's General Physician (GP) to inform them of their patients' participation in the trial and as a reminder of the New Zealand Clinical Guidelines for Stroke Management recommendations to routinely monitor blood pressure and blood lipid levels in stroke patients. The letter includes a request for access to

Table 1 Eligibility screening criteria

Criteria	Eligibility requirement for inclusion
Diagnosis	First-ever stroke, not subarachnoid hemorrhage
Date of stroke	Randomization within six-weeks poststroke
Cognitive impairment	Mini-Mental State Examination (55) ≥23
Mental Health	No current mental health diagnosis and/or receiving current psychological treatment that would affect/contradict motivational interviewing
Involvement in other studies?	No involvement in another study that could affect compliance with treatment or result in significant participant burden
Access to telephone	Has telephone access
Availability	Available to answer further questions in up to 12 months postrandomization
English language	Able to converse fluently in English

these measures by our research team at relevant study time points if required.

Blinding

To reduce measurement bias, follow-up assessments are carried out by individual community-based RAs who are blind to the treatment allocation of the participant and not involved in the delivery of the intervention. At the time of recruitment to the study and prior to each follow-up assessment, study participants are requested not to disclose their group allocation by mentioning any contact with the motivational interviewer to the RA conducting the assessment. Compliance to group allocation blinding will be monitored by the study manager, and reports of unblinding either by participants or research assistants will be recorded as protocol violations, and steps are taken to ensure future assessments are conducted by a blinded assessor for any unblended participants.

MI intervention

The trial intervention is based on the principles of MI as described by Miller and Rollnick (32). To assist the interviewers in adhering to a standardized approach and format when conducting the intervention, an intervention manual has been developed providing guidance for each of the intervention time points and appropriate tools to assist in the interviewing process.

MI interviews are conducted at 28 days, three-, six-, and nine-months poststroke (see flowchart Fig. 1). The first interview is conducted individually face to face. Subsequent interviews are conducted over the telephone whenever possible. MI interviews are to be conducted by an RA who has undergone training in MI and has an understanding of good clinical practice in research. Researchers conducting the interventions are provided with training on the principles of MI by an experienced trainer who is able to demonstrate relevant experience and expertise in this area. RAs were additionally provided training on stroke risk factors, such as diet and nutrition, and medications. As per principles of MI, standard information on cardiovascular disease risk and prevention from the New Zealand Heart Foundation was provided to participants only at their request. Ongoing training and feedback are provided to the MI interviewers throughout the study at regular group and individual training sessions. All training material is saved electronically for future reference. Interviews conducted with participants are recorded, and the de-identified electronic files are available for review by the interviewers and trainer. Ongoing monitoring of the quality and consistency of the MI across all RAs is regularly provided by the MI trainer.

Primary outcomes

Primary outcome measures are (1) change in systolic blood pressure (SBP) and (2) low-density lipoprotein (LDL)-cholesterol levels at 12 months poststroke.

Secondary outcomes

Secondary outcome measures are (1) self-reported adherence to prescribed medications, including self-reported use of antiplatelet/anticoagulant medications, statin, and blood pressure-lowering therapy medications as prescribed (and cross-checked with electronic medication dispense records, where available); (2) self-reported barriers to adherence to medications; (3) cardiovascular events (new stroke or coronary heart disease, both fatal and nonfatal); (4) quality of life as measured by the SF-36 (56); (5) mood as measured by the Hospital Anxiety and Depression Scale (57); (6) change in other blood lipid levels (HDL-cholesterol, total cholesterol, and triglycerides); (7) physical disability as measured by the Barthel Index (58) at 12 months; and (8) healthcare resource consumption and cost effectiveness of the intervention.

Outcome assessments (Table 2) are carried out at 28 days, three-, six-, nine- and 12 months following stroke, with the primary outcome assessment for SBP and LDL-cholesterol carried out at 12 months poststroke. Blood pressure measurements are carried out at six- and 12-month assessments at the participants' place of residence.

Withdrawals and loss to follow-up

Participants are able to withdraw their involvement in the study at any time. The 'intention-to-treat' principle will apply for participants who withdraw from the study or are lost to follow-up, so that data from up to and including their last completed assessment will be included in the analyses.

Data management

Data management services including statistical analyses are contracted to the National Institute for Health Innovation, The University of Auckland. De-identified participant details and data from CRFs are entered into a web-based password-protected database managed by the data management team. All participants

Table 2 Outcome measures and timing of follow-up

	Baseline*	Three-months	Six-months	Nine-months	12 months
From medical notes:					
Demographics (e.g. age, race-ethnicity)	✓				
Type of stroke, stroke severity	✓				
Prestroke lifestyle risk factors (e.g. smoking, physical activity)	✓				
Medical/cardiovascular history	✓				
Blood lipid profile	✓				✓
Blood pressure	✓		✓		✓
Telephone interview					
Short Form-36 (SF-36)	✓	✓	✓	✓	✓
Barthel Index (BI)	✓				✓
Hospital Anxiety Depression Scale (HADs)	✓	✓	✓	✓	✓
Costs (direct healthcare expenditures)	✓		✓		✓
Self-reported adherence and barriers to prescribed medications	✓	✓	✓	✓	✓
Modification of lifestyle risk factors	✓	✓	✓	✓	✓

*Baseline assessments are carried out at 28 days poststroke.

in the study are allocated a unique registration number electronically generated by the database. Paper copies of CRFs and any supporting documentation (including hospital discharge summaries and other relevant medical reports) are de-identified and stored securely, with identifying contact details and signed consent forms stored separately, for seven-years.

Data safety monitoring

An independent Data Safety Monitoring Committee (DSMC) has been established to safeguard the interests of the trial participants, assess the safety and efficacy of the intervention during the trial, and monitor the overall conduct of the clinical trial. The DSMC provides recommendations about stopping or continuing the trial in the event of harm or undue risk to study participants. The DSMC may also make recommendations relating to the recruitment or management of participants, improving adherence to good clinical practice and procedures for data management and quality control. The DSMC group meets on an annual basis or more frequently if the need arises.

Sample size

Four hundred and thirty participants are required to provide 85% power at $\alpha = 0{\cdot}05$ (two sided) to detect a 0·25 mmol/l difference in LDL-cholesterol (SD 0·8 mmol/l), and 80% power to detect a 4 mmHg difference in SBP (SD 14 mmHg), respectively, between UC and MI groups, assuming 10% loss to follow-up.

Statistical analyses

All statistical analyses will be performed using SAS version 9·3 (SAS Institute Inc., Cary, NC). All tests of significance will be two tailed and at 5% significance level throughout the analyses. Baseline characteristics will be summarized and descriptive summary statistics provided for each treatment group. The distribution of all continuous outcomes will be assessed for normality, and skewed data will be subjected to an appropriate transformation before analysis. Continuous data will be analyzed using multiple linear regression if normally distributed and nonparametric analysis if not normally distributed. The change from baseline in each of the repeated continuous outcomes will be analyzed using mixed models and adjusted for baseline value and covariates such as presence of depression as appropriate. Simple incidence rates, relative and absolute risks, and their respective 95% confidence intervals will be calculated for all binary outcomes, and the treatment groups will be compared using chi-squared tests with multiple logistic regression analysis adjusting for other variables as appropriate. In order to check the validity of the missing at random (MAR) assumption, baseline characteristics of those participants with available data and those participants missing data will be compared. The primary analyses will be carried out on an intention to treat basis and mixed models are robust to data that are MAR (55). A per-protocol analysis will be performed to check the robustness of the results where participants with any major protocol violations such as cross-over treatments, withdrawals, and lost to follow-up will be excluded. The consistency of effects for major ethnic subgroups (Māori, Pacific Island, New Zealand Europeans) will also be assessed using tests for heterogeneity.

Cost effectiveness

The cost effectiveness of the study will be determined by comparing the costs and outcomes associated with the control group with the group provided with MI. The costs will include the direct healthcare costs (e.g. hospitalizations, rehabilitation, primary care and outpatient visits, home help and support, and medications). Information on health service utilization is being measured through patient questionnaires and electronic data sources (e.g. medical databases such as the Patient Management System, Accident Compensation Corporation, and Ministry of Health databases matched by individual National Health Index number). In addition, the cost of delivering the intervention will be monitored using a resource-based costing approach that measures the inputs required to deliver the program (e.g. identify time required to recruit, prepare, and deliver the programme, time required to coordinate the care with other providers, distance travelled to deliver the program, etc) and then applying market prices to each of these resources (e.g. cost per hour for the therapist including 50% overheads). This will provide an estimate not only of the net costs associated with the intervention, but also the cost to other organizations interested in adopting MI as part of their standard practice.

Because the intervention is ultimately aimed at reducing the risk of stroke recurrence, the primary outcome variable will be the Quality Adjusted Life Years associated with patients in each arm of the study. Utility scores will be assessed using the EuroQOL 5D, and economic modeling using a Markov Modelling in (TreeAge Pro Suite) 2012 software (TreeAge Software Inc, Williamstown, MA) will estimate the incremental cost effectiveness of the MI group compared with UC by estimating the probability of recurrent stroke based on their SBP and LDL-cholesterol levels at 12 months poststroke. Modeling will be used to extrapolate resource usage (given health services usage and health status) and evaluated over the lifetime of the cohort. Probabilistic sensitivity (using Monte Carlo simulations) analysis will be conducted to reflect the combined implications of uncertainty in the model parameters. Further threshold analysis will be performed to identify under what conditions MI treatment poststroke could be cost effective.

Study organization and funding

The study is hosted at the National Institute for Stroke and Applied Neurosciences at AUT University, Auckland New Zealand. The research is funded by the Health Research Council of New Zealand.

Summary

The MIST study is a randomized clinical trial designed to test the effectiveness of MI for the secondary prevention of stroke. To the best of our knowledge, this is one of the largest clinical trials of MI to be carried out at a population level. This intervention has the potential benefits of being adapted in the community as a cost effective means of reducing stroke burden. In addressing the values and goals of individuals after stroke, MI may present a multifactorial approach to concomitant reduction of risk factors.

Acknowledgements

The authors wish to acknowledge the contribution of the trial participants, the ARCOS IV and MIST study RAs, and medical staff at all the Auckland and Waikato DHBs.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. MIST Data Safety Monitoring Committee and ARCOS IV Steering Committee