Format for Application for ***Ad-hoc*** Research Projects
and
Guidelines for Operation of Extramural Projects

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INDIAN COUNCIL OF MEDICAL RESEARCH

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APPLICATION FOR GRANT-IN-AID OF AD-HOC RESEARCH PROJECT
(Please furnish 30 copies)

Section A
GENERAL

1. Title of the Research Project: **S**econdary **Pr**even**t**i**o**n By Structured Semi-Interactive S**t**roke Prevention P**a**ck**a**g**e** in INDIA (SPRINT INDIA) Study
2. Name and Designation of
   i) Principal Investigators

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3. Duration of Research Project

i) Period which may be needed for collecting the data: 3 years to be extended 5 years

ii) Period that may be required for analyzing the data : **6months**

4. Amount of grant-in-aid asked for (details are to be furnished in Section B)

Total : **538940/- for 7 centers**

1. Study Site: All India Institute of Medical Sciences, Bhubaneshwar

	1st Year
Staff	0
Establishment of Database	0
Developing Workbook, short text messages and stroke education videos with stake-holders***(Oriya)***	50,000
Publishing Workbook *(300 X 2950)*	0
Sending Short messages of 160 characters *(0.5 X 200 X 150)*	15,000
CDs /DVDs /sending mp3/mp4 Short Videos *(10X16X150)*	12,000

Telephone call by Research coordinator for follow-up and queries *(200 minutes X 300)*	15,000
Travel cost for patients for 6months and 1 year visit *(600X 300)*	45,000
Total	**137,000**

2. Study Site: All India Institute of Medical Sciences, Bhopal

	1st Year
Staff	0
Establishment of Database	0
Developing Workbook, short text messages and stroke education videos with stake-holders	0
Publishing Workbook *(300 X 2950)*	0
Sending Short messages of 160 characters *(0.5 X 200 X 150)*	15,000
CDs /DVDs /sending mp3/mp4 Short Videos *(10X16X150)*	12,000
Telephone call by Research coordinator for follow-up and queries *(200 minutes X 300)*	15,000
Travel cost for patients for 6months and 1 year visit *(600X 300)*	45,000
Total	**87,000**

3. Institute of Human Behavior & allied Sciences, Delhi

	1st Year
Staff	0
Establishment of Database	0
Developing Workbook, short text messages and stroke education videos with stake-holders	0
Publishing Workbook *(300 X 2950)*	0
Sending Short messages of 160 characters *(0.5 X 200 X 81)*	8,100
CDs /DVDs /sending mp3/mp4 Short Videos *(10X16X81)*	6,480
Telephone call by Research coordinator for follow-up and queries *(200 minutes X 162)*	81,00
Travel cost for patients for 6months and 1 year visit *(600X 162)*	24,300
Total	**46,980**

4. Fortis Escorts Hospital, Jaipur

	1st Year
Staff	0
Establishment of Database	0
Developing Workbook, short text messages and stroke education videos with stake-holders	0
Publishing Workbook *(300 X 2950)*	0
Sending Short messages of 160 characters *(0.5 X 200 X 81)*	8,100
CDs /DVDs /sending mp3/mp4 Short Videos *(10X16X81)*	6,480
Telephone call by Research coordinator for follow-up and queries	81,00

(200 minutes X 162)	
Travel cost for patients for 6months and 1 year visit *(600X 162)*	24,300
Total	**46,980**

5. Institute of Medical Sciences, Banaras Hindu University, Varanasi

	1st Year
Staff	0
Establishment of Database	0
Developing Workbook, short text messages and stroke education videos with stake-holders	0
Publishing Workbook *(300 X 2950)*	0
Sending Short messages of 160 characters *(0.5 X 200 X 150)*	15,000
CDs /DVDs /sending mp3/mp4 Short Videos *(10X16X150)*	12,000
Telephone call by Research coordinator for follow-up and queries *(200 minutes X 300)*	15,000
Travel cost for patients for 6months and 1 year visit *(600X 300)*	45,000
Total	**87,000**

6. Indira Gandhi Medical College & Hospital, Shimla

	1st Year
Staff	0
Establishment of Database	0
Developing Workbook, short text messages and stroke education videos with stake-holders	0
Publishing Workbook *(300 X 2950)*	0
Sending Short messages of 160 characters *(0.5 X 200 X 81)*	8,100
CDs /DVDs /sending mp3/mp4 Short Videos *(10X16X81)*	6,480
Telephone call by Research coordinator for follow-up and queries *(200 minutes X 162)*	81,00
Travel cost for patients for 6months and 1 year visit *(600X 162)*	24,300
Total	**46,980**

7. Dr. Rajendra Prasad Government Medical College, Kangra H.P

	1st Year
Staff	0
Establishment of Database	0
Developing Workbook, short text messages and stroke education videos with stake-holders	0
Publishing Workbook *(300 X 2950)*	0
Sending Short messages of 160 characters *(0.5 X 200 X 150)*	15,000
CDs /DVDs /sending mp3/mp4 Short Videos *(10X16X150)*	12,000
Telephone call by Research coordinator for follow-up and queries *(200 minutes X 300)*	15,000
Travel cost for patients for 6months and 1 year visit *(600X 300)*	45,000

Total	**87,000**

5. Institution responsible for the research project

Name: **Christian Medical College**
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DECLARATION AND ATTESTATION

i. I/We have read the terms and conditions for ICMR. Research Grant. All necessary Institutional facilities will be provided if the research project is approved for financial assistance.

ii. I/We agree to submit within one month from the date of termination of the project the final report and a list of articles, both expendable and non-expendable, left on the closure of the project.

iii. I/We agree to submit audited statement of accounts duly audited by the auditors as stipulated by the ICMR..

iv. It is certified that the equipment(s) is/are not available in the Institute/Department or these are available but cannot be spared for the project

v. It is further certified that the equipment(s) required for the project have not been purchased from the funds provided by ICMR. for another project(s) in the Institute.

vi. I/We agree to submit (online) all the raw data (along with descriptions) generated from the project to the ICMR. Data Repository within one month from the date of completion /termination of the project.

If any equipment already exists with the Department/Institute, the investigator should justify purchase of equipment.

Signature of the:

a) Principal Investigator _____

b) Co-Investigator(s) _____

c) Head of the Department _____

Signature of the Head of the Institution with seal

Date:

P.S. ICMR should be reminded if no acknowledgement is received within one month from the date of sending the application.

Section - B
DETAILS OF THE RESEARCH PROJECT

Adequate information must be furnished in a brief but self-contained manner to enable the Council to assess the project.

1. **Title of the project.**
   Secondary **Pr**event**io**n By Structured Semi-Interactive S**t**roke Prevention P**ac**kag**e** in INDIA (SPRINT INDIA) Study

2. **Objectives**
   To assess the role of a structured semi-interactive stroke prevention package to reduce the risk of recurrent strokes, myocardial infarction and death in patients with sub-acute stroke after one month

3. **Summary of the proposed research (up to 150 words) indicating overall aims of the research and importance of the research proposal. Application of the work in the context of national priorities of medical research, if any, may also be mentioned.**

Recurrent stroke, cardiovascular morbidity and mortality are important causes of poor outcome in patients with index stroke. According to INTERSTROKE study 80% of strokes are preventable due to presence of modifiable risk factors. However lack of knowledge that stroke and cardiovascular diseases are preventable is major hurdle to reduce the incidence of recurrent stroke and cardiovascular morbidity. This is further compounded by the non-compliance to medications, exercises smoking cessation and other lifestyle modifications.

Stroke awareness has proven to be useful in improving early arrival of stroke patients to emergency thus increasing the thrombolysis rates. Early stroke prevention education using print and audio-visual media may be useful. In addition the use of pervasive mobile phone platform may help us reach patients during multiple intervals in a timely manner.

We aim to use structured semi-interactive stroke prevention package to reduce the risk of recurrent strokes, myocardial infarction and death in patients with sub-acute stroke after one month.

4. **Present knowledge and relevant bibliography including full titles of articles relating to the project.**

Stroke is the second leading cause of death worldwide in 2010.[1]In rural Maharashtra it is the leading cause of death.[2]The Stroke incidence in India ranges from 135 to 145 per 100,000 population. From the recent Ludhiana population based StrokeRegistry[3] and also from the INSPIRE Registry 25% of the patients are below 49 years of age.[4] Hypertension, smoking, alcohol, diabetes, heart disease and lifestyle related problems are the common causes of stroke in India. Rheumatic heart disease and cerebral venous thrombosis are the main etiologies of stroke in the young in our country.

Recurrent stroke

In an Oxfordshire Community Stroke Project reported in 1994, it was found that actuarial risk of suffering a recurrence was 30% (95% confidence interval, 20% to 39%) by 5 years, about nine times the risk of stroke in the general population. The risk was highest early after the first stroke: 13% (95% confidence interval, 10% to 16%) by 1 year, 15 times the risk in the general population. After the first year the average annual risk was about 4%.[5]

In the Copenhagen Stroke Study, [6] stroke was recurrent in 23% despite most of these patients being given prophylactic treatment prior to recurrence. Only 12% of patients with atrial fibrillation were receiving anticoagulant treatment prior to recurrence. In multivariate analysis, recurrence was more frequently associated with a history of transient ischemic attack (TIA), atrial fibrillation, male gender, and hypertension, but not with age, daily alcohol consumption, smoking, diabetes, ischemic heart disease, serum cholesterol, or hematocrit.[6] Mortality was almost doubled compared with patients with a first-ever stroke. In survivors, however, both neurologic and functional outcomes and the speed of recovery were, in general, similar in the two groups. Despite similar neurologic impairments, patients with recurrence contralateral to their first stroke had markedly more severe functional disability after completed rehabilitation than patients with ipsilateral recurrence, implying that the ability to compensate functionally is decreased in patients with contralateral recurrence.[6]

However, recently the rates of stroke recurrence have changed in developed countries. On average, the annual risk for future ischemic stroke after an initial ischemic stroke or TIA is ≈3% to 4%.[7] Recent clinical trials of patients with non-cardio embolic ischemic stroke suggest the risk may be as low as 3%, but these data probably underestimate the community-based rate.[8-12] The estimated risk for an individual patient will be affected by specific characteristics of the event and the person, including age, event type, comorbid illness, and adherence to preventive therapy.[13-15] The current average annual rate of future stroke (≈3%–4%) represents a historical low that is the result of important discoveries in prevention science.[16] These include antiplatelet therapy and effective strategies for treatment of hypertension, atrial fibrillation, arterial obstruction, and hyperlipidemia.

Even in developed nations currently there are large gaps in utilization of preventive drugs, control of risk factors, and uptake of lifestyle-changing behaviors.[17]This is often because of failure in the initiation of secondary prevention.

Novel methods to improve the risk factor control to prevent recurrent stroke

In 2017, the number of mobile phone users is forecast to reach 4.77 billion. The number of mobile phone users in the world is expected to pass the five billion mark by 2019. In 2014, nearly **60** percent of the population worldwide already owned a mobile phone. Mobile phone text messages can be used to remind, encourage, and motivate patients to adhere to secondary prevention strategies, but there has been limited robust scientific evaluation of these interventions.

Using SMS (Short Messaging Service) as reminders to take medicines have been used previously for diseases such as diabetes and HIV with moderate success. **The Tobacco, Exercise and Diet Messages (TEXT ME) trial** was a parallel-group, single-blind, randomized clinical trial that recruited 710 patients (mean age, 58 [SD, 9.2] years; 82%men; 53%current smokers) with proven coronary heart disease (prior myocardial infarction or proven angiographically) between September 2011 and November 2013 from a large tertiary hospital in Sydney, Australia.[17] Patients in the intervention group (n = 352) received 4 text messages per week for 6 months in addition to usual care. Text messages provided advice, motivational reminders, and support to change lifestyle behaviors. Patients in the control group (n=358) received usual care. Messages for each participant were selected from a bank of messages according to baseline characteristics (eg, smoking) and delivered via an automated non-interactive computerized message management system. The primary end point was low-density lipoprotein cholesterol (LDL-C) level at 6 months. Secondary end points included systolic blood pressure, body mass index (BMI),

physical activity, and smoking status. At 6 months, levels of LDL-C were significantly lower in intervention participants, with concurrent reductions in systolic blood pressure and BMI, significant increases in physical activity, and a significant reduction in smoking. The majority reported the text messages to be useful (91%), easy to understand (97%), and appropriate in frequency (86%).[17]**However, the duration of these effects and hence whether they result in improved clinical outcomes remain to be determined.**

The SMS4 stroke trial is a randomized, controlled, assessor blinded single center superiority trial undertaken in Karachi, Pakistan.[18] The participants were randomized into two parallel groups in a 1:1 ratio via block technique with one group receiving the standard of care as per institutional guidelines while the parallel group receiving SMS reminders for each dose of medicine in addition to the standard of care. The intervention group also received twice weekly SMS that reinforced healthy behaviors and the importance of taking medications.[19] Two hundred participants were enrolled. 38 participants were lost to follow-up. After 2 months, the mean medication score was 7.4 (95 % CI: 7.2-7.6) in the intervention group while 6.7 (95 % CI: 6.4-7.02) in the control group. The adjusted mean difference was 0.54 (95 % CI: 0.22-0.85). The mean diastolic blood pressure in the intervention group was 2.6 mmHg (95 % CI; -5.5 to 0.15) lower compared to the usual care group. A short intervention of customized SMS improved medication adherence and effect stroke risk factors like diastolic blood pressure in stroke survivors with complex medication regimens living in resource poor areas.[18] **However it is unclear whether the use of mobile technology will reduce the recurrent stroke by improving the medications adherence and risk factor control.**

Recurrent stroke in India

Data on recurrent stroke and its causes are scarce from low and middle-income countries like India. In the door-to-door survey done in Kolkata 15% of patients had recurrent stroke.[19]

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Stroke. 2007 Mar;38(3):906-10.

5. Preliminary work already done by the Investigator on this problem, e.g. selection of subjects, standardization of methods, with results, if any.

RESTART is a prospective study conducted at Christian Medical College and Hospital from March 2015 to April 2016. All patients with recurrent stroke above 18 years of age were enrolled. Type of stroke, classification of etiology by Trial of Org 10172 in Acute Stroke Treatment (TOAST) and Oxfordshire Stroke Classification (OSCP) and CT/ MR.I finding were collected. Compliance scoring was done using Medication Adherence Questionnaire. A total of 101 (20%) patients had stroke recurrence out of 504 patients screened. The mean age was 64.76 (range 3-85) years and mean recurrent stroke episodes were 2.32 (range 2-5). Among patients with hypertension 82%, diabetes 32% and dyslipidemia 3% were adherent to medications. Thirty two percent of the patients continued to have unhealthy diet and 46% patients continued to take alcohol first stroke. Low compliance score was seen in 58% of patients.

There is also unpublished information from the Ludhiana population based stroke registry. Recurrent stroke cases were collected in addition to first ever stroke from1st August 2012 to 25th March 2013. During this period, a total of 1220 patients were recruited from Ludhiana city and were a total of 166 (13.6%) recurrent stroke cases. Second stroke was 71%, third stroke 23% and fourth stroke 6%. More than 87% of the recurrent strokes were ischemic.

6. **Links with other ICMR projects (ad-hoc, task force or collaborative).**

Establishment of the Indian Stroke Clinical Trial Network
(INSTRuCT)

7. **List of important publications of last 5 years of the all the investigators in the relevant fields (enclose reprints, if available:** Please refer to Section C

8. **Detailed research plan. (give here the design of study, indicating the total number of cases/samples/animals to be studied, the mode of selection of subjects specially in experiments involving human beings, equipment's and other materials to be used, methodology/techniques to be employed for evaluating the results including statistical methods any potential to obtain patents etc.)**

A. Trial Design

The Secondary Prevention By Structured Semi-Interactive Stroke Prevention Package in INDIA (SPRINT INDIA) Study is a multicenter, randomized, parallel-design, adaptive and blinded end-point clinical trial of sub-acute stroke patients. The participants will be block randomized into two groups in a 1:1 ratio, the intervention arm will receive a Structured Semi-Interactive Stroke Prevention Package including patient workbook, short messaging services and health education videos for a period of one-year in addition to standard of care as per current guidelines and control group will receive standard of care as per current guidelines alone.

B. Trial population

Trial site(s) and population(s)

This will be multicenter study conducted at 25 Stroke centers in India. All stroke patients presenting to Stroke and Neurology Clinics, patients admitted in stroke and neurology wards will be screened for eligibility (Appendix 1: 1.Screening Form).

Participating centers are:

1	Christian Medical College, Ludhiana, Punjab	Dr. Jeyaraj D Pandian,
2	All Indian Institute for Medical Sciences, New Delhi	Dr. Vasantha Padma Dr. Rohit Bhatia
3	Postgraduate Institute for Medical Sciences and Research, Chandigarh	Dr. Dheeraj Khurana
4	St Stephens Hospital, New Delhi	Dr. Gaurav Mittal
5	AMR.I Hospitals, Mukundapur, Kolkata	Dr. Jayanta Roy
6	Baptist Christian Hospital, Tezpur, Assam	Dr. Sherly Mary
7	Guwahati Neurological Research Center, Guwahati, Assam	Dr. NC Borah Dr. Rupjyoti Das
8	Nizam Institute for Medical Sciences, Hyderabad	Dr. S Jabeen
9	Lalitha Superspecialty Hospitals, Guntur	Dr. PV Vijaya
10	Government Medical College, Guntur	Dr. Sundarachary
11	Ramesh Hospitals, Guntur	Dr. Kumaravelu
12	Christian Medical College, Vellore	Dr. Sanjith Aaron
13	AMr.ita Institute for Medical Sciences, Kochi	Dr. Vivek Nambiar
14	Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram	Dr. PN Sylaja
15	Kasturiba Medical College Hospital	Brig Dr. SP Gorthi
16	St Johns Medical College, Bangalore	Dr. Thomas Mathew
17	Zydus Hospital, Ahmedabad	Dr. Arvind Sharma
18	BGS Hospital, Bangalore	Dr. Madhu Sudhan
19	GGMC and JJ Hospital, Mumbai	Dr. Pawan Ojha
20	Vadodara Stroke Center, Vadodara Institute of Neurological Sciences, Vadodara	Dr. Anand Vaishnav
21	Narayana Hrudayalaya Hospital, Bangalore	Dr. Vikram Huded
22	CARE Hospitals, Hyderabad	Dr. Dr. Y Muralidhar Reddy
23	National Institute of Mental Health and Neurosciences, Bangalore	Dr. Girish Kulkarni
24	Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry	Dr. Sunil K Narayan
25	Bangur Institute of Neurology, Kolkata	Dr. Biman Kanti Ray
26	Fortis Escorts Hospital, Jaipur	Dr. Neetu Ramrakhani
27	Institute of Medical Sciences, Banaras Hindu University, Varanasi	Dr. Abhishek Pathak
28	All India Institute of Medical Sciences, Bhopal	Dr. Nirendra Kumar Rai
29	All India Institute of Medical Sciences, Bhuvneshwar	Dr. Sanjeev Kumar Bhoi
30	Indira Gandhi Medical College & Hospital, Shimla	Dr. Sudhir Sharma
31	Dr. Rajendra Prasad Government Medical College, Kangra	Dr. Ashish Sharma
32	Institute of Human Behaviour and Allied Sciences, New Delhi	Dr. Suman Kushwaha

C. Eligibility Criteria

Inclusion Criteria

1. Age 18-85 years including both men and women
2. First ever Ischemic stroke or intracerebral hemorrhage

3. Between 2 days-3 months of stroke symptom onset
4. Computed Tomography /Magnetic Resonance Imaging shows recent stroke (infarct and/or hemorrhage)
5. Able to read and complete simple tasks suggested in the stroke work-book if having aphasia or is illiterate, a caregiver is available to read for the patients and complete the reading/work-book tasks for the patients.
6. Able to read and possess a working personal mobile cellular device. In case of patients who is not able to read and/or don't have a personal mobile cellular device or unable to use it, a caregiver is available all times who is able to use mobile cellular devices and read to the patient.
7. Able to watch health education videos on a video player on cellular device or any other video player available to the patient.
8. Able to come for follow up visits for at least 1year
9. Able to provide signed informed consent.

Exclusion Criteria

1. Modified Rankin scale score >4 at the time of enrollment
2. Limited internet and/or mobile accessibility due to travel
3. Patients having active malignancies needing intensive therapy
4. Patients with terminal illness with an anticipated lifespan of less than 1 year
5. Patients with heart failure admitted more than twice in last six months
6. Patients with current psychiatric illness with loss of insight and suicide attempts
7. Patients with cerebral venous sinus thrombosis, aneurysmal subarachnoid hemorrhage, isolated central nervous system vasculitis and systemic vasculitis

D1. Interventions

The study will deliver three interventions.
I. Stroke Prevention Workbook with activities
II. Messaging for Adherence of medication and Health Education via Short messaging Service used by patient or immediate caregiver
III. Health Education Videos to be viewed on cellular device or any other device available to the patients or immediate care giver.

I. Stroke Prevention Workbook with activities

The study team will develop a Stroke prevention workbook according to the Federal Plain Language Guidelines and National Culturally and linguistically Appropriate Services (CLAS) Standards.[20] The main goal would be increasing knowledge by optimizing information processing. The workbook will be developed so that it has as score >90 on CDC Clear Communication Index Score Sheet.[21] This workbook will contain introductory chapters on

Week 1 Stroke
Risk factors of Stroke
Snakes and Ladders
Week 2 High Blood Pressure
Exercise Dairy
Week 3 High Blood Sugar
High Fat in Blood
Week 4 Irregular Heart Beat
Food for Stroke Prevention
Week 5 Exercise to Prevent Stroke

Stop Smoking for a Stroke Free life
Week 6 Living after Stroke
Myths and Beliefs
Game of Truth
Patient Diary
Video Scripts

After each chapter there will be a worksheet which will have series of activities related to that chapter either as questions; fun dice games; treasure hunt on map; identifying things in our house which will increase blood glucose, blood pressure and blood cholesterol; and monthly blood pressure and weekly blood glucose charts.

These chapters and activities will be in local languages and content will be kept simple using regional references. The workbook will be completed by the patients/caregiver in six weeks. Thereafter the patient and caregiver would be requested to read it at least once a month. The study team will call via telephone weekly in first six weeks and thereafter monthly for six months to assess the progress to see if the task were completed. The workbook will remain with the patients throughout the study period and later.

The patients or immediate caregiver will be given a toll-free phone number to call during working hours to clarify doubts and if needed to get additional information (Appendix III: 10.Patient Intervention Diary).

II. Messaging for Improving Adherence of medication and Health Education via Short messaging Service used by patient or immediate caregiver

In the intervention arm patients/caregiver will receive personalized text messages providing reminders for medications, motivation to adopt healthy habits, and health information to improve dietary habits, increase physical activity, encouraging smoking and alcohol intake cessation. The content of the messages will be personalized and decided according to individual risk factors. A catalog of messages will be prepared for stroke, risk factors, and medications. The SMS will be worded according to the Behavior Change Technique Taxonomy (v1) it has 16 clusters components and 93 behavior change techniques.[22]The use of BCTT v1 allows accurate replication; faithful implementation; understanding mechanism of action and systematic review. The catalog was further modified according to the theory of planned behavior, the protection motivation theory and social cognitive theory.[23]Each message will be concise and precise will not exceed 160 characters as described by Friedhelm Hillebrand. The SMS messages will be made in patient's language (Punjabi, Hindi, Telugu, Malayalam, Kannada, Tamil, Gujarati, Marathi and English).

Template of messages

Mr. Vinod, stroke can affect you again, but medicines can prevent it.
Mr. Vinod, smoking can cause stroke, please start to cut back on your cigarettes.
Mr. Vinod, do you know stroke is preventable if you take your medications regularly.
Mr. Vinod, walking for 30 minutes can prevent strokes, did you go for walk today.
Mr. Vinod, did you know excess salt in our food increases blood pressure, which can cause stroke
Mr. Vinod, high blood pressure, diabetes, smoking and high cholesterol levels in body can cause stroke again. Have you taken your medicines to control them?

Participants will receive daily messages for first 6 weeks, thereafter twice weekly for the six months and weekly for the remaining six months. Each message will be sent at a specified time of the day

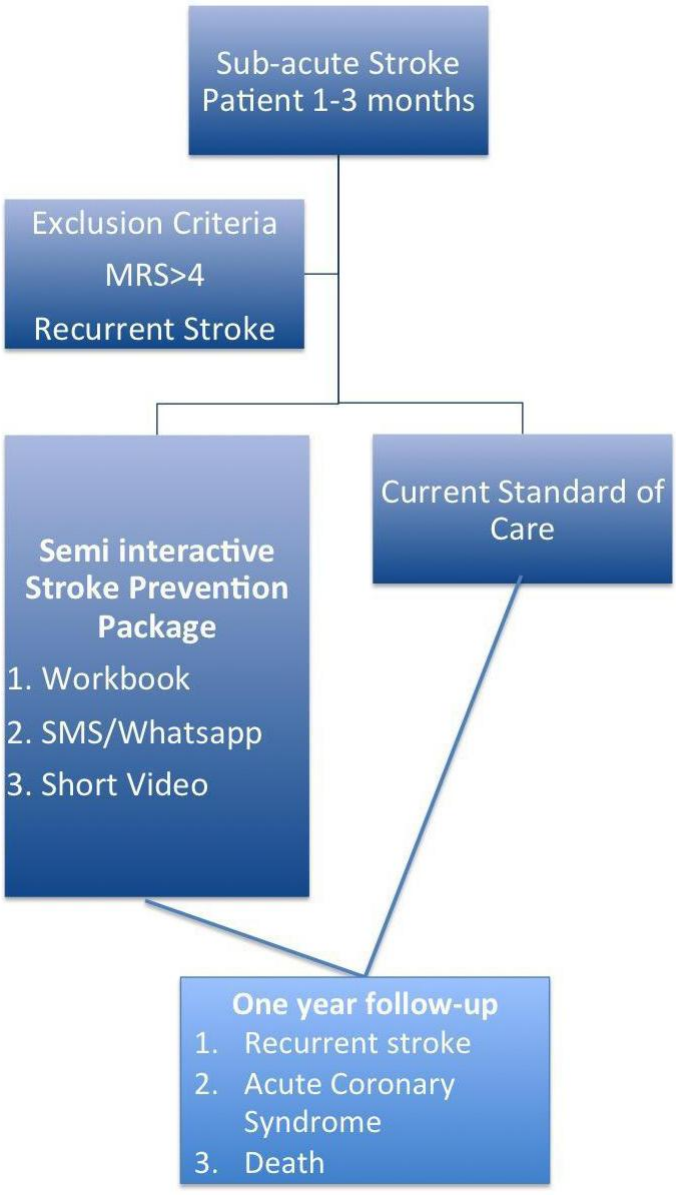
according to patients' preference so that they are most likely to read the message immediately. Patients/Caregiver will be expected to respond to the message by giving a missed call by dialing a call back number as a means of acknowledging receipt of the SMS. So even if there is no Internet/Wi-Fi service available still messages will be delivered.

III. Education Videos to be sent by SMS with a secure, private, unlisted YouTube URL or provided as CDs/DVDs to be viewed at home

Using audiovisual material like videos will enhance the acceptance of behavioral change as the message is more likely to be retained if the patient can identify with the message.[24, 25] The videos will have two purposes

1. Improve knowledge to make informed choices stroke complications, stroke types and prevention.
2. Improving health behavior e.g. taking medication on time, regular exercise and smoking cessation

Each video will be made according to Gagne's theory of Instruction and the component design theory.[26] Further more to make the videos culturally appropriate and acceptable we will design the content according to the Health Belief Model. [27, 28] The few videos will be in form of question and answers with aim of providing direct information and remaining videos will be stories with positive message e.g. if we take medication we have a productive life as an member of society. No videos will highlight negative messages or try to instill fear in patients. Repetition from the stroke workbook will be avoided to prevent avoidance and content will be made more entertaining with stories.



The content will be available in patient languages. Patient will get weekly videos for the first six weeks and followed by monthly videos for remaining study period of 11 months. Patients/Caregiver will be able to see the videos how much every time they want. After viewing for the first time they will be expected to dial the missed call acknowledgement number. If after receiving two consecutive videos patient/caregiver does not respond, the study team member will call patients home to understand if there is any issue receiving the messages, viewing the videos, or dialing the missed call acknowledgement number.

Development of Intervention Package

Stages:

F

1. **Formative Stage**: Developing Preliminary Package
2. **Acceptability Stage:** Refinement with help of stakeholders in all 12 languages
3. **Implementation Stage:** Feasibility study at two centers

Formative Stage: Developing Preliminary Package

The principal investigators have performed literature review on available patient education material from across the world including but not limited to American Heart Association, USA; Heart and Stroke Foundation, Canada; National Institute of Health and Care Excellence, UK; Singapore National Stroke Association, Singapore; Stroke Foundation, Australia and patient Education Resources from World Stroke Organization. The intervention package will be developed at CMC, Ludhiana involving Stroke physicians, Stroke nurses, stroke patients and caregivers. A meeting will be called in first quarter of 2017 to discuss with stakeholders.

The investigators would also consider issues with adherence to medications, as it is one of the most important causes of treatment failure and post stroke poor outcomes. Dr. Jeyaraj has conducted a small study RESTART looking into recurrence rates in index stroke patients. The adherence related issues identified in this study will be incorporated in development of the intervention package. The principal investigators will then develop a portfolio of short messages, possible relatable stories with script to be performed in video and workbook stroke education content/games/activity based on the meeting and content search. At this stage a meeting also will be convened with publishers (Work book) and telecommunication (SMS) experts and mass media (Video content) experts. This preliminary package will be English for the purposes of convenience.

Acceptability Stage: Refinement with help of stakeholders in all 12 languages

The available preliminary package will be then translated in remaining 11 languages. The preliminary package will then be distributed to all the individual language content development centers listed in Table 1.

	Language Development Study Sites	**Languages**
1	CMC, Ludhiana	English and Punjabi
2	AIIMS, New Delhi	Hindi
3	SCTIMST, Thiruvananthapuram	Malayalam
4	NIMHANS, Bangalore	Kannada
5	NIMS, Hyderabad	Telugu
6	CMC, Vellore	Tamil
7	Bangur Institute of Neurology, Kolkata	Bengali
8	GNRC, Assam	Assamese
9	GGMC, Mumbai	Marathi
10	Zydus Hospial, Ahmedabad	Gujarati
11	AIIMS Bhuvneshwar	Oriya

The stroke physician at these sites will then convene a half-day meeting including stroke patients/Caregivers (n=50), Stroke nurses (n=10), Stroke physicians (n=1-2) and Community language experts (n=1). The feedback session will be audio recorded for process evaluation. The content and study will be explained to these stakeholders and intervention will be explained. Post meeting feedback will be taken from the stakeholders and content will be given home. Over period of next one week these stakeholders will review the content in detail and give feedback for acceptability/delivery formats. They will also answer a modified acceptability questionnaire. These

changes from each of ten sites will then be communicated with the CMC, Ludhiana. The changes will be incorporated and prefinal package will be ready for feasibility assessment.

Implementation Stage: Feasibility study at two centers
CMC, Ludhiana and SCTIMST, Thiruvananthapuram will carry out feasibility study including 10 patients/caregivers for a period of one month to assess implementation related issues. The study will assess the acceptability, uptake and retention of the intervention content. The study participants will be assessed with a pre-intervention questionnaire and at the end of one month with post-intervention questionnaire. The questionnaire will be independently answered by the caregivers as well.
A pre and post intervention medication adherence will also assessed with INCA scale.

Treatment in Control Arm

All patients in the control arm will receive standard of care management according to the institutional practice.

D2. Change in dose

As this study does not involve any medication use, there will be no increase or decrease in the dose of the health education delivered. However all medications will be captured in the case record form (Appendix II: Case Record Form)*

11c. Strategies to improve adherence to intervention protocol

All patients/caregiver will receive training regarding the study intervention. They will be guided how they will receive the SMS, how they will be able to read it and respond. The study team member will also introduce the stroke workbook chapters and tasks. Study team member will call patient/caregiver if they do not respond to SMS/ Videos /Workbook tasks.

11d. Permitted Concomitant Intervention and Care.

All patients in the intervention arm and control arm will receive standard-of-care as per current guidelines during the acute period of one month. After one month patient will be seen every three to six months depending on the institutional practice. Patients discharged on urinary catheter and nasogastric tube may require more frequent visits to their treating physicians. The treating physician at no point will try to ascertain if the patient receives study material and message or not. Patients are not permitted to be part other experimental therapy during the study period. (Appendix II: Case Record Form) *

E. Outcome assessment

Primary outcome measure is a composite endpoint of recurrent stroke, high-risk transient ischemic attack, acute coronary syndrome, and death. Stroke will be defined according to the WHO classification as any neurological deficit lasting more than 24 hours due to vascular causes. High risk TIA will be defined as TIA with diffusion restricted lesion of magnetic resonance imaging. TIA patient presenting after few days of event will be assessed with MRI FLAIR sequence /Computed tomography of head. If there is an interval new infarct the event will be labeled as high risk TIA. If the patient was imaged with computed tomography at baseline and they develop high risk TIA and present after three days they should be imaged with CT to allow comparability. Acute coronary syndrome will include unstable angina, non-ST elevation myocardial infarction and ST elevation myocardial infarction proven with appropriate tests including serial cardiac enzymes, electrocardiogram, echocardiogram and coronary angiography. To improve reporting of the primary

outcome measure all patients/caregiver will be required to report the event same day to improve accuracy.

Patient related ***secondary outcome*** **measures** are blood pressure (mmHg), fasting blood glucose (mg/dl), LDL Cholesterol (mg/dl), triglycerides (mg/dl), smoking cessation (No/ total %), alcohol cessation, body mass index, physical activity MET (min/week), medication adherence and modified Rankin scale (mRS) at one year. We will be assessing adherence by three-item Adherence Estimator [29] and INCA scale.[30] The mRS will assessed by a PI[31] at 6 months and one year. (Appendix IV: Assessment Scales)

F. Participant Timeline

Patient with sub-acute stroke will be randomized between 2 days- 3months after symptom onset. Both groups will be followed for a period of one year. In either group patients will visit the attending physician at three months interval. A minimum four non-study routine care visits are expected in each patient during the study period to deliver standard of care. If a patient develops an event (stroke, high risk TIA, acute coronary syndrome and death) he /she will be still followed for a period of one year to assess for additional events.

G. Sample Size Justification

The recurrence stroke data from India is variable (13.6% to 20%). However in a door-to-door survey, recurrent stroke occurred in 15% patients in one year. In study done by Towfighi et al [32], the rate of myocardial infarction in recent stroke patients in two years is 1.4 to 6.34% depending on the Framingham Coronary Heart Disease risk score. In a meta-analysis assessing risk of myocardial infarction (MI) and vascular death after transient ischemic attack and ischemic stroke, annual risk of non-stroke vascular death was 2.1%, non-fatal MI was 0.9% and fatal MI was 1.1%. [33] Taking the two studies into consideration at the end of one year approximately 1-2% will suffer from non-fatal MI. The risk of mortality between one month of symptom onset and one year is 13-15 %. [34,35] The most common cause of mortality in this group after one month is cardiovascular diseases (67.5%) followed by cancer (11.8%) related deaths.[35] Among the cardiovascular deaths after one month index stroke account for 37%, recurrent stroke 36% and coronary artery diseases 26% of deaths.[34]
We expect at least 15% recurrent stroke to occur in one year and an additional 5% to have a combined non-fatal MI and mortality (all cause cardiovascular mortality except recurrent stroke). We aim to reduce the composite endpoint of recurrent stroke, high risk TIA, acute coronary syndrome and death by 3% (a minimum relative change of 15%) from 20% to 17%. Assuming that the rate of composite endpoint in the routine care and intervention arms to be 20% and 17% respectively, to achieve 80% power with alpha error 5%, and an expected 10% drop-outs, a minimum of 2915 is to be recruited in each group.

Adaptive Clinical Trial
The trial will be based on the number of events and will continue to monitor the events in both groups.

Compliance and missing data
All analysis will be done as intention-to-treat.

H. Recruitment Strategies

We are trying to involve 27 centers all over India. Each center admits 300-700 patients per year. Thus we will be able to complete enrollment in three years if each center recruits 7 patients per month.

I. Allocation of interventions

16a Methods for randomization and stratification

Patients will block randomized 1:1 to either intervention arm or routine care arm. We will stratify each group for type of stroke ischemic versus intracerebral hemorrhage to ratio of 6:1. The stratification will be done according to separate block randomization for ischemic stroke and intracerebral hemorrhage.

I1. Methods for concealment of allocation

Web based online randomization will be performed. The allocation will be revealed to site investigators only at the time enrollment from. The allocation will be concealed at all times from the event adjudication committee.

I2. Implementation

The study coordinator will login on website to access the online randomization tool. A pre-specified computer algorithm will generate the allocation for the patient.

J. Blinding

Event Adjudication Committee

A three-member committee of national experts (including two neurologists and one cardiologist) will be provided with event history, examination and investigation in a blinded manner. They will be responsible for classification of event as stroke, high risk TIA, acute coronary syndrome (unstable angina, NSTEMI and STEMI), death and others. All the events will be transcribed to the adjudication committee within 24 hours of the knowledge of the events to the study team.

The trial participants and study team members will not be blinded; however the attending physician will be blinded for allocation. The allocation will not be indicated anywhere on the patient hospital chart. The patients also will be instructed to avoid taking study material to the attending physician's clinic. The study related queries could be asked to the study team members only.

K. Data Collection

At baseline in addition to demographic details, presence of risk factors hypertension, diabetes, dyslipidemia, atrial fibrillation, current smoker, daily alcohol consumption, obesity, lack of physical activity, presence of psychosocial stress, unhealthy dietary pattern and depression would be abstracted on a structured case record form. Also blood pressure, heart rate and rhythm, neurological deficits assessed by National Institute of health stroke scale (NIHSS) and investigations including LDL cholesterol, HDL Cholesterol, triglycerides, prothrombin time with INR in patient taking Coumadin will documented in case record form at baseline. The patient will be then called back at quarterly interval for a total four visits. All centers throughout India will follow similar follow-up regimen. If additional visits are conducted they will documented in the CRF. These events will have to be reported to the national coordinator who in turn will assess if this has caused any bias to the outcome.

During the each follow-up visit NIHSS, mRS, risk factors and medication adherence will be assessed. All patients/caregiver will be instructed report any new events. They will be expected to inform about the event within the first 24 hours.

Post-recruitment retention strategies

All patients will be reminded about the clinic visit at least one week ahead of time. If the patient is not able to come on a particular day then he/she will be adjusted on the next available date. If the patient misses his or her appointment the study team will call home, send letter and if needed arrange a visit at home.

L. Data Management

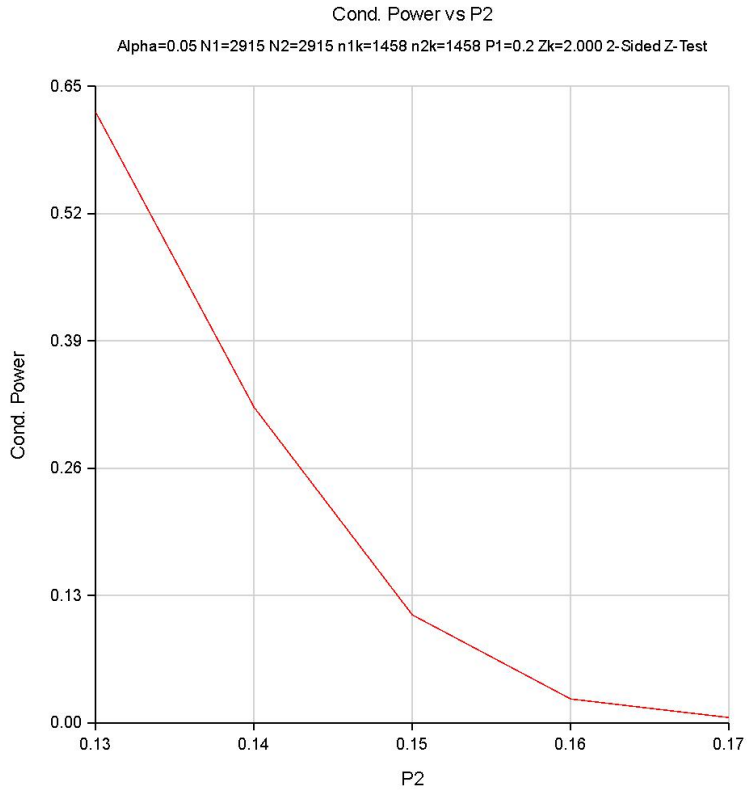
All the data will be entered both on online web portal (The George Institute of Global Health, Sydney) and paper CRF. The national coordinator will conduct a monthly review to assess the data entry accuracy. A screening list will be maintained at each center to assess true effect size of the study.

M. Statistical Methods

We will first compare baseline characteristics in two groups to assess the effect of randomizations. The risk factors are nominal variable and difference will be calculated using Chi Square test. The blood pressure and blood investigations are continuous variable and differences will be assessed using Students‘t’ Test. The primary outcome of the study is nominal variable a composite predefined endpoint and will be analyzed by Chi Square test. A $p < 0.05$ will be considered as significant. Time-to-event analysis will be done by Kaplan Meier survival curve at one year. The secondary outcome measure including reduction in blood pressure, drop in LDL cholesterol, triglycerides will be analyzed using ANCOVA. Smoking and alcohol cessation will be assessed using Chi Square test.

Interim futility analyses

The study team will conduct one interim analysis after 50% enrollment i.e., 1458 patients in each group .[34] The first 1458 of 2915 subjects in treatment group and 1458 of 2915 in control group achieve a 32% conditional power to detect a difference of -6% at a significance level of 0.05 using a two-sided test. The value of the proportion in control group is 20% and the value of test statistic is 2. The futility index is 0.37. The DSMB will decide finally regarding futility or efficacy of the study during the interim analysis.



N. Data Monitoring

In SPRINT INDIA study a three-member independent data safety and monitoring committee (DSMB) will be formed by ICMR.. The DSMB will oversee the interim analysis after 50% enrollment.

O. Safety monitoring and adverse events

All events including the adverse events in the study will be adjudicated by the EAC (Appendix II: Event Adjudication Committee Form)*.

9. **Facilities in terms of equipment, etc, available at the sponsoring institution for the proposed investigation.**
   A. Clinical Research Centre: Conducting national and International clinical trials for more than 10 years
   B. Stroke Imaging facilities including Computed tomography and Magnetic resonance imaging
   C. Stroke Clinic: Weekly Stroke Clinic with 20-25 patients
   D. Stroke Unit: Active Stroke Unit for last ten years.
   E. Stroke Expertise: Two Stroke Clinician Scientists

10. Budget requirements (with detailed break-up and full justification): given separately
    (i) **Staff:** The research coordinator recruited for the INSTRuCT Task Force will be involved in the project this will lead to no added cost for the project.
    (ii) Contingencies
    Recurring: In the study we will be developing and distributing a stroke workbook and stroke education videos. We will also develop and send short

messages of 160 characters. These will be sent to all 5900 patients. The cost involved in each item has been enlisted in the table below.

Non-recurring:

Developing educational videos will involve script writing, recording in studio, editing and storing. A total 16 videos will be made.

Developing Workbook will involve meeting with publishers to develop a durable quality book and formatting of the content in acceptable form for the patients and caregivers.

The SMS will be developed involving local linguistic experts. Atleast one meeting will be held at 1 different sites for checking the accuracy of content according to regional culture

We expect the approximate cost of printing the intervention workbook (durable and acceptable format, plastic coated pages with markers to write) to be around Rupees 300 each.

Travel: Patients will be have to visit twice for the study purposes and will be given Rupees Three HunDr.ed for each visit towards transport. They will have to produce a transport receipt of the same amount or more to avail this benefit.

Regular Telephone calls will be made by the research assistant to the patients to assess compliance of therapy. We expect atleast 200 minutes of conversation per patient including patients who are not in intervention group.

*Appendix II: Case Record Form

Form Number	Case Record Form
2	Randomization Form
3	Patient Demography Form
4	Baseline Form
5	Follow-up Form 6 months
6	Follow-up Form 1 year
7	Primary Outcome Form
8	Serious Adverse Form
9	Event Adjudication Committee Form
11	Patient Information Leaflet
12	Patient Communication Form
13	Patient Feedback Questionnaire