System-integrated technology-enabled model of care to improve the health of stroke patients in rural China: protocol for SINEMA—a cluster-randomized controlled trial

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Background Despite the significant burden of stroke in rural China, secondary prevention of stroke is suboptimal. This study aims to develop a SINEMA for the secondary prevention of stroke in rural China and to evaluate the effectiveness of the model compared with usual care.

Methods The SINEMA model is being implemented and evaluated through a 1-year cluster-randomized controlled trial in Nanhe County, Hebei Province in China. Fifty villages from 5 townships are randomized in a 1:1 ratio to either the intervention or the control arm (usual care) with a target to enroll 25 stroke survivors per village. Village doctors in the intervention arm (1) receive systematic cascade training by stroke specialists on clinical guidelines, essential medicines and behavior change; (2) conduct monthly follow-up visits with the support of a mobile phone application designed for this study; (3) participate in virtual group activities with other village doctors; 4) receive performance feedback and payment. Stroke survivors participate in a health education and project briefing session, receive monthly follow-up visits by village doctors and receive a voice message call daily as reminders for medication use and physical activities. Baseline and 1-year follow-up survey will be conducted in all villages by trained staff who are blinded of the randomized allocation of villages. The primary outcome will be systolic blood pressure and the secondary outcomes will include diastolic blood pressure, medication adherence, mobility, physical activity level and quality of life. Process and economic evaluation will also be conducted.

Discussion This study is one of very few that aim to promote secondary prevention of stroke in resource-constrained settings and the first to incorporate mobile technologies for both healthcare providers and patients in China. The SINEMA model is innovative as it builds the capacity of primary healthcare workers in the rural area, uses mobile health technologies at the point of care, and addresses critical health needs for a vulnerable community-dwelling patient group. The findings of the study will provide translational evidence for other resource-constrained settings in developing strategies for the secondary prevention of stroke. (Am Heart J 2019;207:27-39.)

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Background

Stroke is the leading cause of deaths and disabilities in China with about 1.5-2 million new stroke cases each year and a total of about 7.5 million stroke survivors.[1,2] The most recent estimation showed that stroke led to about 18.5% of deaths in China and was the largest contributor to the loss of disability-adjusted life years in 2016.[3] The incidence, prevalence, and mortality of stroke in rural China have all surpassed those in urban areas in recent years.[4] In addition, recurrent stroke constitutes a relatively high proportion of all preventable stroke in China.[2] Among stroke survivors, the first-year recurrence rate is 11.2%, signifying the importance of secondary prevention of stroke.[5]

The main pillars of effective secondary prevention of stroke include lifestyle modification and evidence-based

pharmacological treatments. These strategies have been extensively researched,[6-8] endorsed by clinical guidelines,[9,10] and proposed by WHO guidelines as cost-effective approaches for stroke patients in resource-constrained settings.[11] However, access to even essential care is highly variable and the quality of evidence-based care is far below China's guideline recommendations, especially in rural areas and despite the large and growing disease burden from stroke.[12-14]

There are several barriers that results into the suboptimal implementation of recommended secondary prevention of stroke in rural China. From the healthcare system's point of view, the key barriers include fragmentation of acute-oriented care, low technical and educational capability of primary care providers, and lack of awareness and incentives for secondary prevention.[15] Currently, there is no specific strategy to deliver follow-up services to stroke patients after acute stages in rural China. Village doctors provide primary healthcare services to the rural population under the management of township health centers; however, the quality of services is relatively poor.[16] Although there is no solution to address all of these rural health system barriers, strengthening the primary healthcare system by capacity building to improve the quality of services have been recognized as an effective strategy for improving the prevention and control of chronic conditions.[17]

Patients' awareness and health behaviors also contribute to the suboptimal secondary prevention of stroke in rural China. With rapid urbanization, rural communities in China are left behind with large number of older people who are vulnerable. They have relatively poor health conditions and receive limited insurance protection through the China's New Cooperative Medical Scheme.[18] Lacking awareness of the self-management of chronic conditions and economic difficulties result in poor adherence to secondary prevention. The PURE China study compared cardiovascular patients in urban and rural communities and found that the adherence to healthy lifestyles and the use of secondary prevention drugs are lower among cardiovascular patients in rural communities than in urban settings in all regions with different economic development levels.[19] A study based on the China National Stroke Registry also showed that only 46.2% of the stroke patients continue the use of prescribed secondary prevention drugs after 3 months post hospital-discharge, and the persistence of use was positively associated with younger age, higher family income and the hospitals where the patients received treatment.[20]

Mobile health (mHealth) technologies, in the form of text messaging and mobile applications, have emerged as a promising approach to support behavior change among both the providers and patients.[21] Studies showed that mHealth technologies can empower patients' self-management of chronic conditions, increase access to healthcare services for vulnerable population, enhance communication flow, and improve the delivery of training to healthcare workers.[22-26] However, despite the ubiquitous mobile network coverage and high penetration rate of mobile phones, few mHealth interventions have been implemented in rural China. The feasibility and effectiveness of such interventions is worthy of investigation.[27]

To improve community-based stroke care and outcomes among stroke survivors, we developed a system-integrated technology-enabled model of care (SINEMA) for the secondary prevention of stroke in rural China. The model was designed on the basis of our previous studies in rural China[28,29] and further refined through extensive contextual research. The SINEMA model is currently being implemented and evaluated through a 1-year cluster-randomized controlled trial in fifty villages which were stratified randomized in a 1:1 ratio to either the intervention arm or the control arm in Nanhe County, China.

This paper describes the contextual research and the development of the SINEMA model, and presents the protocol for the SINEMA trial used to evaluate the effectiveness of the model. Reporting of the protocol adheres to the SPIRIT guideline[30] (Appendix 1 is the SPIRIT checklist).

Methods

Study site

This study is being conducted in Nanhe County, a county in Hebei Province, China, with an intention to generate solutions that can be adapted in other resource-limited settings. Nanhe County is located on the stroke belt of China, an area marked with a comparatively high prevalence of stroke.[31] It is a "provincial poverty county" with an annual disposable income per capita as 11,030 RMB (less than half of the average national annual disposable income per capita).[32] In Nanhe County, there are 2 county-level hospitals, 8 township hospitals and 218 village clinics (one for each village). The capacity of these healthcare facilities is relatively limited, and the health system is fragmented across primary, secondary and tertiary healthcare facilities. Most stroke patients receive acute care in hospitals equivalent or above county level when they have urgent stroke events. Follow-up care after hospital discharge is minimal to none-existent. Access to the Internet, nevertheless, is widespread, and cell phone (including both feature phone and smartphone) ownership among adults is high (>90%).[33] A survey conducted among rural residents in Hebei Province found that 94.7% participants owning a mobile phone and about half of them surf the internet through the mobile phone.[34]

Contextual research, development of M-health system and pilot study

Contextual research. Before the main trial, the research team visited the local communities 3 times and

Table I. Key results of contextual research and SINEMA ways to address the barriers

Barriers	SINEMA ways to address
Village doctors	
Low adherence to clinical guidelines on the secondary prevention of stroke	Capacity building and training by specialists
Low health information technology and low educational capability	Use of digital health technology (SINEMA APP)
Lack of incentives for secondary preventive care	Providing performance-based incentives to village doctors
Stroke survivors	
Uncontrol of blood pressure due to poor medical adherence (Main factors related to poor medication adherence include lack of awareness, forgetfulness and economic difficulties.)	Monthly follow-up visits by village doctors Health education on medication adherence through voice message
Poor physical functioning due to lack of physical activity and rehabilitation	Health education on physical activity through voice message
Illiteracy and health illiteracy	Use of voice message call
Physicians at township and county hospitals	
Fragmentation of care	Support and communication across different tiers of health facilities through training and project management
Over-burden of specialists	Task-sharing by primary healthcare workers
Specialists at tertiary hospital in Beijing	
Experienced in stroke treatment but not familiar with rural situation	Rely on the train-the trainer to train model The training material is localized by specialists from county hospital

conducted 49 in-depth interviews with stakeholders including physicians at township and county hospitals, village doctors, stroke survivors and family caregivers. Through the contextual research, the research team identified key challenges faced by both healthcare providers and stroke survivors, and the potential solutions for addressing the barriers, which informed the design of the SINEMA model. Table I shows the key results from the contextual research and the approach that the SINEMA model could be applied for addressing the barriers. The SINEMA model is designed to address the system barriers through strengthening the capacity of the village doctors through training and support, and to shift the tasks of post-acute stage management from tertiary hospital to community-based primary healthcare settings. The SINEMA model also emphasizes patients' self-management by promoting patients' awareness and knowledge on the secondary prevention and adherence to the preventive treatments. Thus, we expect that the SINEMA model is able to improve the access and quality of the secondary prevention of stroke among rural patients.

Development of the SINEMA APP and voice message dispatching system. Based on the results from the contextual research, the SINEMA APP development team (consisting of clinical, technical and public health experts) designed a mHealth system for this study and future scale-up, which consists of an android-based APP used by village doctors and a voice message dispatching system customized for stroke survivors. The APP was developed using Java language, on the server side with the Spring MVC and iBATIS framework together with MySQL database with data encryption. The SINEMA APP for village doctors contains modules facilitating self-training on secondary prevention of stroke, set reminders of follow-up visits, guide the follow-up visit data collection as part of intervention, as well as displays performance indicators. The APP is also linked with a third-party voice message dispatching system through its application server. After uploading the messages to the third-party platform by the research team, messages containing reminders and health education information can automatically be sent to participants based on the designed algorithm. In addition, township and county project officers can monitor village doctors' performance through the APP as a function of quality control. (Appendix 2 shows the overall structure of the SINEMA mHealth system).

Pilot study and finalization of SINEMA model. After testing the feasibility of the SINEMA model in a 3-month pilot study conducted in 4 villages, we modified and finalized the SINEMA model to target blood pressure control, medication adherence, and physical activity. The SINEMA model (Figure 1), cognizant of health system's organization around primary, secondary and tertiary healthcare levels in China, adopts the principles of cascade training with feedback and task-sharing, and relies on existing human resources available at the community level. It also proposes the use of innovative mobile technology as tools (in the form of an Android-based SINEMA APP for village doctors and cellphone voice messages for participants). The overarching aim is to strengthen the capacity of village doctors on delivering services for the secondary prevention of stroke and promoting medication adherence and physical activity among stroke survivors.

Trial design and protocol

Trial overview. The SINEMA trial is a cluster-randomized controlled trial to evaluate the effectiveness of a system-integrated technology-enabled model of care to improve the secondary prevention of stroke in Nanhe

Figure 1

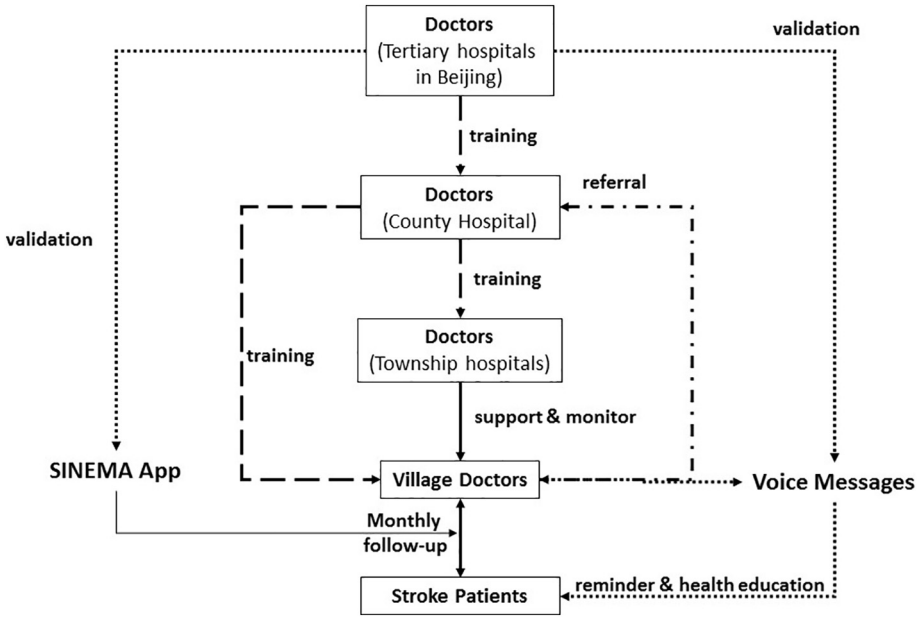


Diagram of the SINEMA Model.

County, a rural area of Hebei Province, China. Fifty villages from 5 townships are stratified randomized in a 1:1 ratio to either the intervention arm (implementing SINEMA model) or the control arm (usual care). Our target sample size was to prospectively enroll 25 participants per village with recruitment of a about 1250 participants (see sample size calculation below).The trial duration for each participant is 1 year. Figure 2 shows the trial flow chart.

Study population

Selection of township and villages. We selected 5 out of the 8 townships of Nanhe County based on their demographic and economic conditions, and township leaders' willingness to participate in our study. The top 5 townships where there are the greatest number of the villages with a minimum population size of 1500 were selected to participate in the study. In each township, we selected 12 villages from each township as eligible villages where the number of population ranks at the top with a minimum population size of 1500. In each village, we asked village doctors to screen the stroke survivors in their villages based on health records and their best knowledge and generate a list of potential participants. To reach the targeted sample size, we selected and recruited 10 villages from each township according to the number of stroke survivors screened and village doctors' willing to participate in the study.

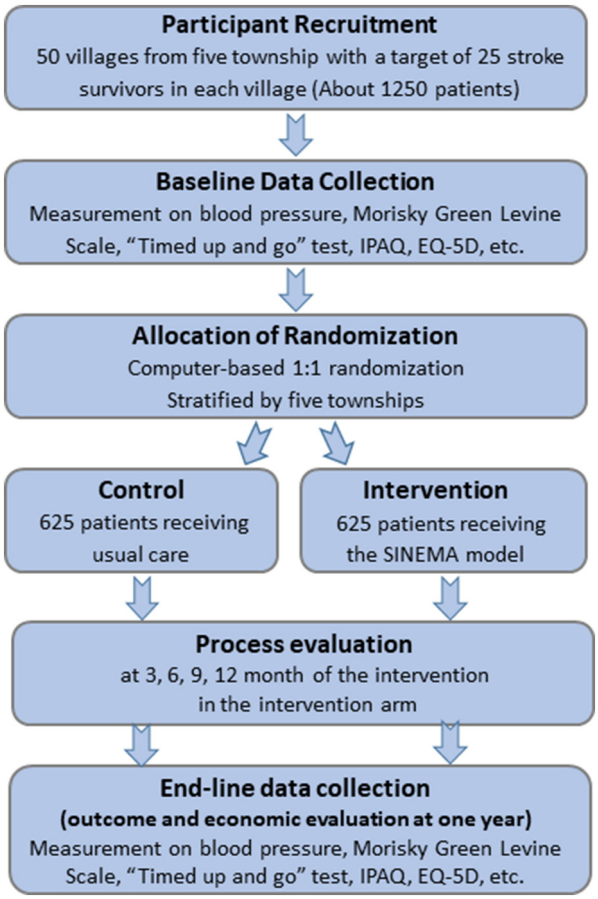
Selection of village doctors. For each village, 1 village doctor was selected who is an officially certified village doctor and can stay in the village for at least 4 days per week in the next 12 months, as well as knows how to use a smartphone and agrees to participate in the study. If there is more than 1 eligible village doctor in the village, the leader of the village clinics was selected.

Selection of participants. Stroke survivors meeting the following criteria were recruited to form the study sample: those who are over 18 years old, have a history of stroke (including ischemic and hemorrhagic stroke) diagnosed at county hospital or higher-level facilities, are currently in a clinically stable condition and not receiving acute stroke treatment, will live in this village for at least 9 months during the next 12 months, have basic communication ability (i.e. can understand simple instructions) and give their informed consent. Exclusion criteria are: patients who are unable to get out of bed without maximum assistance, have serious life-threatening disease such as cancers or an expected life span of less than 6 months.

Recruitment of participants. The recruitment were conducted village by village. Eligible stroke patients were invited to participate in the study by village doctors. If there were less than 30 screened stroke survivors in the village, all screened stroke survivors were invited. If there were more than 30 screened stroke survivors, 30 stroke survivors were randomly selected and invited by village doctors. Recruitment were conducted by trained research staffs in the village clinics. All patients were informed and provided written consents before participating in the study.

Randomization. The purpose of using a cluster randomized design is to reduce the contamination and

Figure 2



SINEMA Trial Flow Chart.

improve the practical feasibility for implementing the intervention protocol.[35,36] The 50 villages were randomized in a 1:1 allocation ratio to the intervention or control arm with stratification by the 5 townships. Randomization was conducted by an independent biostatistician at Duke University who was not part of the study. Within each township (strata), a uniform random number between 0 and 1 was generated for each of the 10 villages, the numbers were sorted in increasing order and then the first 5 and second 5 villages were labeled "A" and "B", respectively. Finally, a virtual coin flip was performed to assign one of "A" and "B" to intervention and the other to usual care.

The randomization was conducted independently of the participants' recruitment and baseline survey. Both research staffs and village doctors who were involved in the recruitment and baseline survey were blinded of the randomization. The allocation of the intervention and control arm was released to village doctors and the implementation team in each township after all study participants in the township had been enrolled and completed the baseline survey. The Appendix 3 showed the Timeline cluster diagram[37] of the trial.

Intervention and control. The intervention arm will implement the SINEMA model for 1 year, which consists of a provider-facing intervention aiming to strengthen the capacity of village doctors in delivering stroke secondary prevention, and a stroke survivor-facing intervention aiming to promote medication adherence and physical activity.

Provider-facing intervention includes the following components:

1) Systematic cascade training for village doctors: Systematic training will be provided based on "train the trainer to train" model. All the training materials were drafted based on the clinical guidelines[9] by experienced stroke specialists from tertiary hospitals with adjustments to suit the knowledge level and learning abilities of village doctors. Training consists of an initial 1-day training session on stroke clinical guidelines, essential medications, strategies for using Health Belief Model to promote medication adherence and physical activity, and the intervention protocol. Only village doctors who pass the test after the initial training can take part in the intervention. A 3-hour refresher training session will be provided at the 3-months after the intervention begins.
2) Monthly follow-up visits with the support of the SINEMA APP: village doctors in the intervention arm are provided with the SINEMA APP, designed for this study to standardize the flow of the monthly follow-up visit. With the assistance of SINEMA APP, during each monthly follow-up visit, village doctors will collect information about participants' health conditions, medication use, blood pressure level, etc.; and provide health education to participants on medication adherence and physical activity.
3) Village doctor group activities: Every week, a village doctor group activity will be organized through *WeChat*, an extremely popular smartphone-based messaging and social media APP in China. During the group activity, village doctors share their experience in follow-up visits and project implementation, report concerns to the research team, and seek support from the research team or their peers.
4) Performance feedback and incentives: An appropriate amount of payment is offered to village doctors determined by the number of follow-up visits conducted. In addition, an incentivizing bonus for good performance and quality will be offered. The factors considered include the quality of data that village doctors collected through APP, number and quality of responses in *WeChat*, results of the on-site supervision by the research team, etc.

To improve the medication adherence and physical activity of stroke survivors, our stroke survivor-facing intervention program includes the following components:

1) Briefing session: A briefing session was organized in each village in the intervention arm. During the session, the research team introduced the SINEMA project, provided a brief health education session on the importance of blood pressure control, medication adherence and physical activity.
2) Monthly follow-up visits and follow-up handout: Every month, participants will be visited by their village doctors who are equipped with SINEMA APP with a standard flow of follow-up visit. During the follow-up visit, participants will be educated about their blood pressure level, the importance of medication adherence and physical activity. Participants will also be provided with a handout designed specifically for stroke survivors with low literacy showing their blood pressure level, their medication prescription and their goal of physical activity as a tool for them to adhere to doctors' prescription.
3) Voice messages for health education: Participants in the intervention arm will receive 1 voice message at 7 AM every day. The message contains information to remind them to take their prescribed medication and be physically active. A message bank of 365 messages was designed by research team, verified by stroke specialists and rural doctors based on the Health Belief Model, modified to suit the goals and context of stroke survivors in rural China.

Villages in the control arm continue their usual practice without the introduction of any of the SINEMA activities described above. For the villages in the control arm, there is no specific healthcare service focusing on stroke patients. Village doctors provide both clinical services (including but not limited to blood pressure tests and medicine prescription based on the needs of patients when patients walked in the clinic) and basic public health services (including 4 follow-up visits per year among people with hypertension and diabetes as required by the government).[38]

Quality assurance and control. To ensure the quality of the intervention, several key measures will be taken: (1) Township managers (a staff from township hospital) and county project officer (a staff from the Health Bureau of Nanhe County) will monitor the progress and the quality of village doctors' follow-up visits via the SINEMA APP. Township managers will communicate with the village doctors on the issues they noticed and provide the information to the research team as records; (2) County project officer and township managers will call 3 patients per village per months to audit the follow-up visit they received. The list of patients will be randomly generated by the SINEMA APP; (3). The research team will conduct quarterly on-site supervision and half-year auditing on adverse events.

In addition, we have several strategies to avoid the contamination of the intervention activities. The project management team will only invite study participants in the intervention arm to join training and briefing sessions and name of the participants will be verified before each session. In addition, the smart phone application will be provided only to village doctors in the intervention arm with a unique log-in account. The research team will also verify the phone numbers of participants in the intervention arm to ensure that the voice messages will only be delivered to participants in the intervention arm. The only foreseeable way in which treatment contamination could occur is by intervention participants discussing lessons learned with control participants. Such likelihood is small because they are located in different villages. As noted above, participants in the control group will not have access to any elements of the intervention. Thus, we are able to eliminate or minimize contamination through our cluster randomization design as opposed to individual randomization.

Data collection. We will invite participants in both the intervention and control arms to visit the village clinics to receive a comprehensive survey and standard anthropometric measures at baseline and the end of the study (12 months). The data collection will be conducted following a standard protocol by trained staff recruited from the Center of Disease Control and Prevention (CDC) of a nearby county, who are completely blinded of randomized allocation of villages and will not be involved in the implementation of the intervention. For patients, a brief interviewer-administered questionnaire will be completed using Qualtrics, an online-survey platform, which is able to ensure the quality of data through setting the format and force response. The questionnaire will collect data on demographic information, disease history, medication use and adherence, lifestyle behaviors, and utilization of healthcare services including hospitalization. Patients will have a physical examination comprising of assessment of blood pressure, weight, height, waist circumference and the "Timed Up and Go" test.

Village doctors will be invited to complete a self-administered knowledge-attitude-practices questionnaire including questions regarding their demographic characteristics and clinical practice experience. The survey consists of 6 questions regarding their knowledge on the secondary prevention of stroke guidelines and 17 questions regarding their attitude and practice in delivering the stroke secondary prevention to patients evaluated by using 5-Likert scale.

Data on hospitalization and recurrence of stroke will be collected through extracting the data from county medical insurance system and death record system. Data on hospitalization will be extracted every month from the medical insurance system, which includes the reason and duration of the hospitalization. Death data will be extracted through the death report from the local CDC and verified through a smartphone-based shortened version of verbal autopsy survey administered by county

Table II. The schedule of enrollment, intervention and assessments

	STUDY PERIOD								
	Enrollment	Baseline Assessment	Allocation of treatment arms	Post-allocation					Close-out Assessment
\TIMEPOINT	*-3 mon*	-2 mon	0 mon	*0 mon*	*3 mon*	*6 mon*	*9mon*	*12mon*	*13 mon*
ENROLMENT:									
Eligibility screen and recruitment	X								
Informed consent	X								
Randomization *	X								
Allocation of treatment arms			X						
INTERVENTIONS:									
Systematic Cascade training for village doctors				X	X				
Village doctors' Monthly follow-up visits to patients				←	—	—	—	→	
Village doctor group activities				←	—	—	—	→	
Performance feedback and incentives for village doctors				←	—	—	—	→	
Briefing session for participants				X					
Daily voice messages for participants				←	—	—	—	→	
OUTCOME ASSESSMENTS:									
Systolic blood pressure		X							X
Mobility		X							X
Medication adherence		X							X
Physical activity level		X							X
Quality of life		X							X
Stroke recurrence		X							X
Hospitalization		X		←	—	—	—	→	X
Morbidity and mortality						X			X
Village doctors' knowledge, attitude and practice on the secondary prevention of stroke		X							X
PROCESS AND ECONOMIC ASSESSMENTS:									
Process evaluation					X	X	X		X
Cost of intervention				←	—	—	—	→	X

Table III. Outcome variables in baseline and follow-up survey

Outcomes	Measures	Methods
Outcomes for participants:		
Primary outcome:	Systolic blood pressure	Electronic BP monitor*
Secondary outcome:	Diastolic blood pressure	Electronic BP monitor*
	Mobility	The "Timed Up and Go" test[40,41]*
	Physical activity level	Questionnaire: IPAQ short form[43]*
	Medication adherence	Questionnaire: Morisky Green Levine Scale[42]*
	Quality of life	Questionnaire: EQ5D[44]*
Exploratory outcomes:	Stroke recurrence and hospitalization	Questionnaire and medical insurance records**
	Stroke related disability	Questionnaire: modified Rankin scale**
	Stroke related mortality	Death records and verbal autopsy ***
Outcome for village doctors:	Knowledge, attitude and practice of village doctors	Questionnaire self-administered by village doctors

Note:
*The outcomes for participants will be measured by trained staff recruited from Center of Disease Prevention and Control of a nearby county, who are complete blinded of randomized allocation of villages and will not be involved in the implementation of the intervention.
**Data will be collected through extracting information from medical insurance records.
***Data on mortality will be collected through extracting information from death records and verified by a smartphone-based shortened version of verbal autopsy survey.

project officer to family members of dead participants in this study. The survey has been proved to be feasible and acceptable in rural north China.[39] Respecting the culturally appropriate grieving period, the interview will be conducted at the sixth and twelfth month after initial of the intervention. Table II shows the overall data collection procedures based on SPIRIT guideline.

Outcome evaluation. The primary outcome is systolic blood pressure (SBP) of participants. The effectiveness of the program will be evaluated by the SBP at 1-year follow-up between the intervention and the control arm. Blood pressure is measured on the right upper arm (or left arm if the right arm is disabled) with participant seated after 5 minutes of rest using an electronic blood pressure monitor (Omron HEM-7052). Two measurements are taken, and the mean value is calculated. If the differences between the 2 SBP is larger than 10 mmHg, a third measurement is conducted, and the mean value of the only or the last 2 reading is calculated. Secondary outcomes include participants' diastolic blood pressure, mobility, medication adherence, physical activity level and quality of life. Mobility is measured using the Timed Up and Go test, a simple and quick functional mobility test that requires the participants to stand up, walk 3 meters, turn, walk back, and sit down.[40,41] Medication adherence is measured using the 4-item Morisky Green Levine Scale with scores ranging from 0 to 4 with a higher score indicating lower medication adherence.[42] Participants will respond to the 4 questions with yes or no for each type of medicines (anti-hypertension, aspirin and statin) if they were prescribed by the physicians before.[42] Physical activity level is measured using the short version of the International Physical Activity Questionnaire (IPAQ).[43] Participants were asked to recall the frequency and duration of rigorous activities, moderate activities and walking they performed in the past 7 days. Quality of life is measured using EuroQol-5 Dimensions-5L (EQ5D).[44] Exploratory outcomes include stroke recurrence, hospitalization, disability and mortality, which will be collected through questionnaire or medical insurance records. (See Table III).

Sample size. Based on a sample of 1,250 prevalent stroke patients in 50 villages (with 25 villages per arm and on average 25 patients per village), assuming loss of 2 clusters (villages) per arm and loss of 1 patient per village on average, an intra-cluster correlation coefficient (ICC) of 0.04 (a conservative assumption), and a standard deviation (SD) for SBP pre-post change of 20 mmHg, the study has 83% power (with 2-sided alpha = 0.05) to detect a 5 mmHg net difference in pre-post change of SBP between intervention and usual care arms. Previous studies have been demonstrated that a 5mmHg difference is a meaningful change for stroke recurrence in 3-5 years.[45] The effect size of a 5mmHg difference corresponds to a standardized effect size of 0.25 (5/20) and therefore we will have more than 80% power to detect such standardized effect sizes for secondary outcomes of interest, assuming the same level of clustering of those outcomes.

Statistical analysis. A comprehensive statistical analysis plan will be published in a separate manuscript with the key details provided here. In brief, analysis will be performed using participant-level outcome data and will take into account the stratified and clustered design. The intention to treat principle will be adopted whereby all participants are analyzed in the intervention arm to which they were assigned even if they did not receive any SINEMA services in the intervention arm or if they accessed SINEMA services in the control arm (something that is unlikely to happen due to the SINEMA APP and SINEMA voice messages will only available to participants in the intervention arm). Continuous variables will be reported as mean and standard deviation if symmetric or as median with 25^{th} and 75^{th} percentile if not. Counts and proportions will be reported for categorical variables.

Summary of baseline to 1-year follow-up changes in continuous outcome variables will also be reported.

The mixed effects model framework[46] will be used to model continuous outcome variables, with a random intercept for cluster (to account for the cluster randomized design) and fixed effects for strata (to account for stratification).[47] More specifically, the outcome variables will be the baseline to 1-year follow-up changes which will be regressed on baseline levels of the outcome to gain statistical power. Additional analyses will be performed that additionally adjust for baseline covariates that are identified as being imbalanced by chance. If model assumptions are violated for continuous secondary outcomes, alternative approaches will be considered including variable transformations (e.g. log-transformations for potentially skewed variables such as timed-up-and-go scores) or robust standard errors for skewed outcome variables. Categorical outcome variables will be analyzed using the generalized estimating equation approach in order to obtain population-averaged intervention effects and to account for the clustered design.[47,48] As for analysis of continuous outcome measures, all the generalized estimating equation (GEE) analyses will account for the stratified by including fixed effects for strata. The modified Poisson GEE approach (with log-link) will be used to obtain risk ratios for binary outcomes.[49] Multi-category outcome variables will be modeled using multinomial logit GEE to obtain odds ratios. Robust standard errors will be used to account for potential model misspecification. All analyses will be conducted blinded so that the treatment arm is not revealed until all results have been generated.

Although the trial is designed to minimize missing outcome data at 1-year follow-up through monthly contacting participants in the intervention arm and contacting participants in the control arm at the sixth month, there is the possibility of loss to follow-up, as in all longitudinal studies. To identify baseline covariates that are related to loss to follow-up and whether treatment arm is related to loss to follow-up, we will summarize baseline characteristics and treatment arm by loss to follow-up status (i.e. lost to follow-up vs. not lost to follow-up) and will separately summarize the same baseline covariates for each treatment arm in order to identify possible differences by arm.[50,51] If we identify baseline covariates that are predictive of loss to follow-up so that the missing outcome mechanism appears to be of a covariate-dependent missing form, we will adjust for these covariates in the mixed effects regression models in order to account for this mechanism. Such an approach has been demonstrated to perform well in simulation studies and avoids the need for computationally expensive imputation procedures.[52,53] Similarly, for GEE models, in order to conserve the population-averaged interpretation, we could use weighted GEE to account for the missing outcomes whereby observed outcomes are reweighted according to an inverse probability weight for the probability of being observed at the 1-year follow-up time point. If loss to follow-up is not negligible, we will also consider implementing the pattern mixture approach to test for sensitivity to our missing data assumptions.[54]

In addition, given that the SINEMA intervention is a multicomponent intervention, there is the possibility of different level of fidelity to the intervention. Given the challenges of defining protocol violations in this context, we will use a strategy that is commonly adopted in trials of complex, multicomponent interventions, namely we will describe and summarize levels of adherence to the intervention activities among participants according to the different components of the intervention, rather than formally define degrees of fidelity in advance. Thus, we will separately characterize fidelity or protocol violation and report the fidelity related information for the intervention arm. Fidelity indictors on patients' side includes: the proportion of follow-up visits that village doctors have completed on the basis of the overall required monthly follow-up visits, the number of training session attended and the number of messages sent in the virtual group. For stroke patients, we will calculate the proportion of voice messages responded and the proportion of doctor visits made.

Process evaluation. Four waves of process evaluation will be conducted in the intervention arm at the 3rd, 6th, 9th month from the initial intervention and the last one after the 1-year intervention to document how the SINEMA intervention is implemented and to explore the essential components of the intervention. Face-to-face in-depth interviews with key stakeholders involved in the study including patients, village doctors, doctors at township level, study coordinators, county government officials will be conducted by independent investigators. A standard interview guide will be developed, and all interviews will be recorded, transcribed and analyzed before the beginning of the follow-up survey, to avoid prejudice in interpretation. We will also try to reach village doctors if participants from their village discontinue from the intervention to understand the factors related to their lost to follow-up.

Economic evaluation. The economic evaluation will have a trial-based evaluation and a modeled evaluation of long-term cost and effectiveness. We consider costs from the perspective of health services instead of the societal perspective because the aim of the study focuses on how SINEMA model could solve healthcare related issues and stroke survivors are already being in the community with very few of them have official and stable work post-stroke. Thus, pension costs and worker productivity are not as relevant to our study design. Data on costs of the intervention such as study design, APP development and incentives for the village doctors, will be collected from project financial reports. Data on the cost related to utilization of health care services and medications will be collected at the 1-year follow-up surveys. This

information will be supplemented by insurance claims data focusing on both inpatient and outpatient costs. For the trial-based evaluation, cost effectiveness will mainly be assessed using 2 indicators: cost per unit reduction in systolic blood pressure and cost per unit increase in quality adjusted life year (QALY). To capture costs and outcomes beyond the trial, a decision-analytic model will be developed to enable long-term outcomes to be simulated, which will draw on the literature and available databases. Sensitive analysis will be conducted to determine the robustness of the estimates.

Current trial status. The township and village selection and participant screening were conducted in May 2017. The participants' recruitment was started on June 22. By the end of July 2017, the recruitment is completed with 50 village doctors and 1299 stroke survivors from 50 villages in 5 townships of Nanhe. After the baseline survey, villages were randomly allocated into intervention and control arm. Currently, the SINEMA model is being implemented in 25 villages (covering 637 stroke survivors and 25 village doctors) in the intervention arm.

Discussion

Combating the increasing burden of stroke and implementing effective secondary prevention strategies in resource-constrained settings is a global health priority.[55,56] The SINEMA study aims to implement the system-integrated technology-enabled model of care, using a behavior change theory, for the secondary prevention of stroke in rural China and to evaluate the effectiveness of the model through a cluster-randomized control trial. To the best of our knowledge, this trial is one of very few studies that aim to rigorously evaluate a complex, yet pragmatic approach, for the secondary prevention of stroke in resource-limited settings.[57,58] The findings of the study will not only provide evidence on the feasibility and effectiveness of the SINEMA model, but they will also provide translational evidence for other resource-constrained settings.

Resource-limited areas often encounter tough challenges in providing high-quality essential care for stroke patients including system-level barriers. The design of the SINEMA model attempts to change the secondary prevention of stroke at the system level. Through capacity building, the SINEMA model shifts the task from overburdened specialists at tertiary or secondary healthcare facilities to primary healthcare providers in the community and promotes a continuum of care by integrating different tiers of healthcare systems. Studies demonstrated that task-shifting from specialists to front-line healthcare workers is effective in improving the healthcare delivery in resource-limited settings, though most of previous studies focused on infectious diseases with few studies targeting the management of chronic diseases.[59-61] In rural China, there are about 1.19 million village doctors working in the rural clinics with basic medical training and equipment.[62] Equipping these human resources with skills and knowledge on the secondary prevention of stroke has the potential to shift the current acute-oriented care to a more comprehensive and integrated care in rural China.

The intervention is designed to be innovative but feasible at the individual level (healthcare providers and patients) with enablement by mHealth technologies. There is growing evidence showing smartphone or tablet based system can improve the healthcare delivery and services.[21] Considering the high penetration of android phone among village doctors, we incorporate the designed SINEMA APP into the intervention aiming to empower the capacity of village doctors and fulfill their complex needs of managing patients, recording information, getting feedbacks, and receiving trainings with the same platform. In terms of intervention among patients, studies for improving self-management of chronic conditions have utilized technologies ranged from text-message reminders to biosensors.[63] Given the ubiquitous mobile network coverage and near ubiquity of mobile phones in China, we deliver the intervention partially through voice messages with the expectation of providing the intervention to all vulnerable population including illiterate patients.

The design of the intervention and APP was informed by extensive contextual research conducted. To ensure the feasibility of the study, we modified the intervention to emphasize medication use and physical activity rather than focusing on all aspects of stroke related risk factors (such as diet and smoking). Studies showed that 94% of the Chinese burden of stroke is attributable to the combined effects of modifiable metabolic and behavioral risk factors. Among all modifiable risk factors, hypertension, dyslipidemia and lack of exercise were significantly associated with ischemic stroke and hypertension was associated with hemorrhagic stroke.[64] Another strength of our study is the rigorous design of a cluster-randomized controlled trial with comprehensive outcome, process, and economic evaluations. The process evaluation conducted throughout the whole study will provide significant information regarding the enablers and barriers in delivering and receiving the SINEMA intervention, which will provide insights for understanding study results and practical knowledge for scaling up the intervention. Economic evaluation will support policy making that adheres to cost-effective principles.

Our study also has some potential limitations. First, we considered systolic blood pressure as primary outcome instead of the stroke recurrence or stroke related mortality due to the study duration and limited funding. Nevertheless, previous studies showed that blood pressure is strongly predictive of stroke outcomes and commonly used in many trials.[7,45,65] It is non-invasive

and can be objectively measured. Second, there could be some potential selection biases introduced through the recruitment stage and we need to be cautious in interpreting the results or generalize to other populations. Although all villages in the county are very similar in culture, economic development, socio-demographic characteristics and disease burdens, we recruited relatively larger villages to ensure a balanced and sufficient cluster size. Moreover, although village doctors have a very close relationship with most of residents in the villages, it is possible that some stroke survivors were not invited because their disease history was not known to village doctors. Although these selection biases during the recruitment stage could not be eliminated, we believe that the magnitude of the biases was small and our sample is still a representative sample of typical larger-size villages in Nanhe County. The randomization based on clusters will make sure that there is no differential effect on the 2 arms due to any potential selection biases. In addition, although a total of 50 villages from 5 townships were involved in the study, our study was conducted in only one county (Nanhe County in Hebei Province). The generalizability of the study results may be limited. However, the SINEMA model has been designed with sustainability and scalability in mind from the outset and is expected to be able to be adapted to other resource constrained settings. Thirdly, to make the case generalizable to most of the situations, we did include owning and being able to use a cell-phone as an inclusion criterion during the recruitment stage. It is likely that some participants may face difficulties in receiving the voice calls due to physical disability or sharing a phone with family members. However, the participants will still be able to receive other interventions from the village doctors. We will analyze and report voice call uptake data as one of the indictors for the fidelity of the intervention.

As one of the few studies investigating the models in improving the secondary prevention of stroke in resource-constrained settings, this study has both national and global implications. Although preventing stroke has become a priority in China since 2009, most of the strategies currently implemented focus on improving stroke registry, establishment of specialized stroke care unit, improvements in emergency care and acute stage treatment.[66,67] Studies on secondary stroke prevention in rural settings are very scarce. Few studies investigate strategies for the secondary stroke prevention in urban China,[68,69] but these projects are not feasible for rural settings where the healthcare resources are constrained and cannot provide evidence for the long-term care among large numbers of stroke survivors living in villages. The lessons learned through implementing SINEMA study will be very important for future research in the field and policy makers in developing strategies for the secondary prevention of stroke in rural China. We also expect this study will yield significant translational findings for the design, implementation and scale-up interventions for the secondary prevention of stroke in other resource-limited settings.

List of abbreviations

SINEMA system-integrated technology-enabled intervention
mHealth Mobile Health
APP Application
IPAQ International Physical Activity Questionnaire
EQ5D EuroQol-5 Dimensions-5L
CDC Center of Disease Control and Prevention

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Declarations

Ethics approval and consent to participate

The trial was registered at the clinicaltrials.gov (NCT03185858). The trial protocol received ethics approval from the institutional review boards at Duke University, USA and Beijing Tiantan Hospital, China. The pilot study received ethical approval from the institutional review board at Duke Kunshan University, China. All participants provided written informed consent when they were recruited to participate in the study.

Authors' contributions

EG, WG, CS, and LLY drafted the manuscript. EG, WG, CS, JB, ET, YW, LX, BO, AAB, ZL, YZ CL, and LLY, contributed to the study concept and conceived the study design. All authors provided critical revision of the manuscript and approved the final manuscript. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

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