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Study protocol: A Randomized Parallel-controlled Study on The Effectiveness and Cost-Effectiveness in Screening Gait Disorder of Silent Cerebrovascular Disease Assisted by Artificial Intelligent System versus Clinical Doctors (ACCURATE-1)

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ABSTRACT

Introduction:

Silent cerebrovascular disease (SCD), which is a common disease in the elderly, leads to cognitive decline, gait disorders, depression, and urination dysfunction, and increases the risk of cerebrovascular events. Our study aims to compare the accuracy of the diagnosis of SCD-related gait disorders between the intelligent system and the clinician; thus, our team developed an intelligent evaluation system for gait. This study proves whether the intelligent system can help doctors make clinical decisions and predictions, which aids the early prevention and treatment of asymptomatic cerebrovascular diseases.

Methods and analysis:

This study is multi-centered, prospective, randomized and controlled.

SCD subjects aged 60–85 years in Shanghai and Guizhou will be recruited continuously. All subjects were randomly divided into a doctor with intelligence assistance group or a doctor group, at a 1:1 ratio. The doctor and intelligent assistant group will accept the intelligent system evaluation, while the doctor group will accept the clinicians' routine treatment procedures. Meanwhile, all subjects will accept the panel's gait assessment and recognition rating scale as the gold standard.

Ethics and dissemination:

Approval was granted by the Ethics Committee of Zhongshan Hospital affiliated with Fudan University on November 26, 2019. The approval number is B2019-027(2) R. All subjects signed an informed consent form before enrollment. Serious adverse events will be reported to the main researchers and ethics committees.

Trial Registration Number: NCT04457908

Key words:

Adult neurology, Stroke, Health economics

Article Summary

Strengths and limitations of this study

Our study aims to compare the accuracy of diagnosing SCD-related gait disorders between the intelligent system and clinicians.

This study evaluates the effectiveness and equity of intelligent systems to diagnose SCD-related gait disorders compared to clinicians.

Follow-up was not involved in this study.

INTRODUCTION

Silent cerebrovascular disease (SCD) is very common in the elderly, and often incidentally found by cranial imaging [1]. It presents as a lacunar infarct, white matter hyperintensities (WMH), and microhemorrhages on imaging; however, patients do not have acute symptoms. Reports on the prevalence rate of SCD varies, mainly due to the selection of different sample populations. Furthermore. there is a lack of relevant studies for people under 45 years of age. Approximately 25% of those over 80 years of age have SCD[2]. Leary[3] et al. found that more than 11 million people in the United States were newly diagnosed with cerebral infarction or hemorrhage on imaging, but only 770,000 of them had clinical symptoms. SCD is mostly related to age and vascular risk factors (hypertension, diabetes, smoking, obstructive sleep apnea-hypopnea syndrome, migraine, etc.). This indicates that vascular lesions play an important role in SCD, but the specific pathophysiological pathways need to be further explored. SCD lacks the symptoms of an acute neurological impairment; thus, it is often overlooked by patients and doctors. Nonetheless, it is also associated with chronic neurological impairments. Multiple studies have shown that SCD can lead to cognitive decline, gait disorders, depression, and urination dysfunction, and may increase the risk of future cerebrovascular events[4-6]. Debette[7] et al. assessed the incidence of stroke, dementia, and death in 2229 community patients (mean age 62±9 years), and found that SCD patients had increased risk of stroke (heart rate [HR]: 2.84, 95%CI :1.32 to 6.10), and dementia (HR: 6.12, 95%CI :1.82-20.54), which were independent risk factors. Stroke results in high medical costs. Shelby[8] et al. analyzed the hospitalization cost for patients with cerebrovascular events in 137 community hospitals. Patients with SAH had the highest cost ($23,777, n=1,124), followed by patients with intracerebral hemorrhage ($10,241, n=3,139), ischemic cerebral infarction ($5,837, n=18,740), and transient ischemic attack ($3,350, n=7,861). The length of stay was 11.5 days for intracerebral hemorrhage, 7.5 days for intracerebral hemorrhage, 5.9 days for ischemic cerebral infarction, and 3.4 days for transient ischemic attacks.

Early detection of subtle neurological impairment in SCD and standardized intervention can help improve patient prognosis and reduce costs. At present, the diagnosis of SCD mainly relies on the imaging and clinical expertise of doctors, which may be subjective and leads to misdiagnosis.

Therefore, the use of an intelligent system for early quantitative evaluation of

neurological damage in SCD can reduce the evaluation time and differences between individuals. Moreover, it may allow doctors to make sound clinical decisions and outcomes using this algorithm. It also consequently helps in the early prevention of SCD and guides diagnosis and treatment while reducing medical costs.

METHODS AND ANALYSIS

Study Design

ACCURATE-1 is a multicenter, prospective, randomized controlled study. (Figure 1) Subjects are randomly divided into a doctor and an intelligent assistant group, and a doctor group at a 1:1 ratio. The doctor and intelligent assistant group accepts the intelligent system evaluation, while the doctor group accepts the clinician's (neurology attending/resident, and/or accepted neurology standardization training of medical attending/resident) routine treatment procedures. Meanwhile, all subjects accept the panel's gait assessment and recognition rating scale as the gold standard. Data on patient demographic characteristics, socioeconomic status, medical history, neurological function assessment, laboratory examination, imaging examination, quality of life, health services utilization and their unit costs, and other social costs will also be collected.

Setting

The trial was conducted in 14 hospitals in Shanghai and Guizhou, including secondary and tertiary hospitals. All staff members of the trial were trained.

Participants

In this study, subjects with SCD aged 60 to 85 years in Shanghai and Guizhou will be recruited continuously. All subjects will sign an informed consent form. After recruitment, eligible subjects will be selected for the study according to the inclusion and exclusion criteria.

The inclusion criteria are as follows:

- Aged 60 years to 85 years.

- Diagnosed with SCD/silent stroke, according to the 2016 statement issued by the American Heart Association (AHA) and American Stroke Association (ASA):
  - No clear previous history of stroke or clinical symptoms, which failed to attract clinical attention.
  - A lacunar infarct of vascular origin was defined as a subcortical round or ovoid fluid-rich lacunar lesion with a diameter of 3–15 mm, showing low central signal and irregular marginal high signal on T2-flair. The central signal is similar to that of the cerebrospinal fluid, while the distribution is consistent with the blood supply area of the perforating artery. Fazekas scores should be ≥2 points.
  - WMH of vascular origin defined as a high signal on T2-flair in the white matter area (periventricular or subcortical). Fazekas scores should be ≥2 points.
  - Cerebral microbleeds defined as a small, round, empty focus of signal flow on an SWI or T2-weighted image, 2–10 mm in diameter. The number of microbleed lesions should be ≥5.
  - Cranial magnetic resonance imaging (MRI) shows at least one of the following within one year and should provide Digital Imaging and Communications in Medicine (DICOM) data.
- Conscious and able to complete cognitive assessment.
- Able to stand and walk independently and complete gait assessment without assistance.
- Sign the informed consent.

The exclusion criteria are as follows:

- Intracranial lesions have been clearly diagnosed as a demyelination disease, leukodystrophy, intracranial space-occupying lesions, autoimmune encephalitis, etc.
- Gait disorders have been diagnosed with Parkinson's disease, normal cranial hydrocephalus, otogenic diseases, subacute combined degeneration, peripheral neuropathy, osteoarthritis, and lumbar diseases.
- Cognitive disorders have been diagnosed as Alzheimer's disease, frontotemporal dementia, Lewy body dementia, etc.
- Severe neurological diseases such as previous cerebral trauma, epilepsy and myelopathy, etc.
- Severe cardiovascular complications which cannot tolerant the assessment.
- Severe visual or hearing impairment, aphasia, cognitive disorder, gait disorder, etc., which cause uncooperative cognitive and gait assessment.
- Refusal to participate in the study.
- Other anomalies that could not be included in the exclusion criteria, but we considered inappropriate to be included in our study.

Study procedure

Appropriate subjects will be selected based on the inclusion and exclusion criteria. Clinical data collection by doctors will be collected based on their demographics, medical history, neurological function assessment, laboratory examinations, imaging tests, quality of life, health service utilization, socioeconomic status, and medical and other social costs. The entire data collection process will be recorded only for data verification and monitoring.

Whether the subject's cranial MRI meets the inclusion criteria will first be determined by trained doctors according to the STRIVE standard. The committee of experts,

including clinical radiology experts and image post-processing technology personnel, will review the DICOM data. Subjects who do not pass the review will be excluded accordingly.

Subjects in the doctor and intelligent assistant group will be evaluated for neurological function by using the following intelligent system test: the time up and go test (TUG). It is used to evaluate the subjects' gait function, which requires them to stand up from their seat and walk straight forward for 3 m, turn back and walk straight back to the chair, and then sit down again. Using simple cognitive evaluation (mini-cognitive assessment) screening of the subjects' memory and executive function, the participants will first be asked to remember three unrelated words and immediately repeat these three words. Afterwards, they are asked to draw a clock with 12 numbers and a pointer to 3:40, then asked to recall the three words. The verbal function of the subjects will be assessed using verbal retelling items in the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). Subjects will be asked to repeat "44 stone lions," "I only know Zhang Liang came to help today," and "the cat always hid under the sofa when the dog was in the room" in Chinese. The intelligent system will access the subjects' gait characteristics (get up, turnaround time, stride length, step velocity, stride length, step width, etc.), language features (pronunciation, intonation, word order, wrong language, language fluency, etc.), and clock features (circle, number, pointer).

Subjects in the doctor group will undergo routine medical procedures. The doctor group is required to comprise of attending or resident physicians in neurology and/or attending/resident physicians receiving standardized training in neurology. The physician will register his/her professional qualifications, relevant knowledge training experience, educational background, and working years. The physician will determine whether the subjects have gait disorders through routine medical procedures such as their present and previous medical history and physical examination data.

The video of the TUG test of all subjects (including the doctor group and the doctor and intelligent assistant group) will be evaluated by two specialists in movement disorders as the gold standard. Specialists will be blinded to the grouping. The expert physician will judge the subjects' gait based on their clinical experiences. The results

will be divided into normal and abnormal gaits. If the results are different, the opinion of a third expert will be included.

All subjects will be evaluated based on the following scales under the guidance of a trained doctor: 1) MMSE: evaluates time and place orientation, immediate and delayed memory, attention and computation, naming, retelling, listening comprehension, reading and expression, and visual-spatial ability, with scores ranging from 0 to 30; 2) MoCA: evaluates visual space, executive function, naming, memory, attention, language, abstraction, and orientation, scores ranging from 0 to 30; 3) Color word test (CWT): evaluates semantic activation, dominant response inhibition, attention, working memory, information processing speed, etc.; 4) Digit span test (DST): evaluates immediate memory and attention; 5) Verbal fluency test (VFT): evaluates language capabilities; 6) TUG test: evaluates the total time subjects will take to complete it, with the average value obtained after three repetitions; 7) 10 m walking test (10 MWT): The subjects will walk 10 m in a straight line at normal walking speed, while the time and number of steps required for the subject to complete the 10 MWT will be recorded, with the average value obtained after three repetitions, and 8) Tinetti performance-oriented mobility assessment (TinettiPOMA): This includes balance and gait tests, with a maximum score of 28. A score between 19 and 24 indicates a risk of falling, while a score below 19 indicates a high risk of falling.

All subjects will be evaluated using the EQ-5D, which describes the quality of life of the subjects.

To evaluate the cost-effectiveness from the healthcare system and the societal perspectives, we will collect the data of unit costs and utilizations of the equipment, medications, and labor hours taken to deliver each individual diagnosis, as well as cost of patients' accommodations, transportation, and productivity losses due to their disease. The labor hours taken will be collected through a questionnaire for staffs, while the equipment cost (intelligent system) will be amortized over its estimated lifespan. The medication and other patient costs will be collected using a patient questionnaire. (Table 1)

Table 1. Assessment of two groups.

Assessment	Doctor & intelligent assistant	Doctor
Intelligent TUG test	×	
Intelligent Mini-cog test	×	
Intelligent sentence repetition test	×	
Routine treatment procedure		×
Panel's gait assessment	×	×
TUG	×	×
10MWT	×	×
TinettiPOMA	×	×
MMSE	×	×
MoCA	×	×
CWT	×	×
DST	×	×
VFT	×	×
EQ-5D	×	×
Fall condition	×	×
Utilization and unit cost	×	×

× indicates that the assessment took place. TUG, time up and go test; Mini-Cog, Mini-Cognitive Assessment ;10 MWT, 10m walking test; TinettiPOMA, Tinetti performance-oriented mobility assessment; MMSE, Mini-Mental State Examination; MoCA, Montreal cognitive assessment; CWT, Color word test; DST, Digit span test; VFT, verbal fluency test.

Assessments

Outcome measures

The primary outcome is the sensitivity of the intelligent system and clinicians to screen for gait disorders.

The secondary outcomes are as follows: 1) the specificity, coincidence, and the Yoden index of the intelligent system and clinicians to screen for gait disorders; 2) the positive and negative predictive values of the intelligent system and clinicians at different levels to screen for gait disorders, and 3) healthcare costs of intelligent systems and clinicians to screen for gait disorders, and the incremental cost effectiveness ratio (ICER) will be estimated by cost per additional true case detected using an intelligent system versus clinicians.

Sample size

This study is a 1:1 superiority trial. Referring to the preliminary study of gait disorder in SCD and our group, we expect that the sensitivity of doctors and intelligent assistants will be 85%, while the sensitivity of the doctor group will be 68%. The power is 1-β =80%, with a significance level of α=0.05. According to our calculations, there should be 94 positive cases evaluated by the gold standard in each group. The expected shedding rate is 6%; therefore, each group required 100 positive cases. Considering that the positive rate of gait disorder in the population is approximately 20%, a total of 1000 subjects should be included.

There are 14 sub-centers for the two regions in our study, including three secondary and three tertiary hospitals in Shanghai, and four secondary and four tertiary hospitals in Guizhou. The expected ratio of patients in secondary and tertiary hospitals is 1:2; in principle, no less than 30 subjects should be enrolled in each center, and 400 subjects for each region.

Randomization

Stratified blocked randomization will be used in this study. Stratification factors included regions (Shanghai and Guizhou), and hospital levels (secondary and tertiary hospitals). All subjects meeting the inclusion criteria are randomly divided into a doctor and intelligent assistant group and a doctor group at a 1:1 ratio through the central randomization system.

Data analysis

The normality was tested with the Shapiro–Wilk test. Continuous data with a normal distribution are expressed as the mean ± standard deviation. Data with non-normal distribution are presented as medians with interquartile ranges. A t-test or non-parametric test will be used to compare continuous data. Count data are expressed as frequency (%). For comparison of categorical variables, the chi-square test, Fisher's exact probability test, or CMH chi-square test will be used. Subgroup analyses will include region and hospital levels. A significant difference was considered to be statistically significant at $p < 0.05$. Statistical analyses were performed using the SAS 9.4.

A cost-effectiveness analysis will be conducted from a healthcare system and a societal perspective; all the costs and diagnostic outcomes will be listed separately, then the incremental cost will be calculated per true case additionally detected by using the intelligent system versus the clinicians. We will explore the possibilities of conducting a long-term cost-effectiveness analysis using economic decision modeling based on future cost savings and health gains by using the intelligent system versus clinicians to screen for gain disorder.

Patient and public involvement

Each patient voluntarily participated in the study and signed the informed consent. Each subcenter recruited patients according to the inclusion criteria and competed for enrollment. Patients didn't involve in the design of this study. Patients don't need to assess the burden of the intervention. The result of this study will be disseminated via peer-reviewed journals.

DISCUSSION

Our study aims to compare the accuracy of the diagnosis of SCD-related gait disorders between the intelligent system and the clinician. Furthermore, we aim to evaluate the effectiveness and equity of intelligent systems to diagnose SCD-related gait disorders compared to clinicians.

Early identification of the characteristic gait of SCD is helpful for clinical diagnosis and treatment. Studies have found that the deterioration of neural gait disorder is often associated with impaired cognitive function, which can serve as a warning sign of dementia. Rosso[9] et al. reported that after a 14-year-follow-up, gait slowing was associated with cognitive impairment in the elderly population (OR per 0.1 s/y slowing 1.47; 95% CI, 1.04–2.07). After nine years of follow-up, Dumurgier[10] et al. found that 296 of the 3,663 subjects developed dementia, in which a decreased pace was associated with an increased risk of dementia, with a HR value reaching 3.39 for every 0.007 m/s decrease in pace [95% CI 1.37-8.43]. Therefore, early quantitative gait analysis will help in the early detection of cognitive impairment. Appropriate interventions are needed to improve patient outcomes and prognoses.

However, the assessment of gait and cognitive function mostly depends on the visual or scale method used by doctors. Due to the lack of a unified evaluation process, the results are relatively random and inconsistent. To the best of our knowledge, this is the first study to analyze gait features in SCD based on an intelligent system. Using an intelligent system allows a reduction in the evaluation time and differences between individuals, thereby increasing early diagnosis and prevention of SCD.

Currently, no studies have explored the effectiveness of SCD screening in reducing adverse health events or cost-effectiveness[1]. Although SCD may cause dementia and increase the incidence of stroke, the absolute risk is not high. Therefore, screening requires a low-cost and highly efficient test method. Artificial intelligence (AI) is a good choice. We will investigate the human, material, and financial costs of physicians and artificial intelligence in different regions when assessing a patient's neurological function. We hope that our intelligent system can reduce the cost of SCD screening and improve diagnosis in remote areas.

Ethics and dissemination

The subjects' rights will be protected according to the regulations of the China Food and Drug Administration, the Declaration of Helsinki, and the International Conference on Harmonization - Good Clinical Practice (ICH-GCP). The subjects'

data will be kept strictly confidential. The results will be disseminated in peer-reviewed journals.

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Authors' contributions

Xin Wang, Jing Ding contributed to the conception and design of the study. Min Hu and Jin Zhao contributed to the design of the health economics part. Beini Fei, Yanmin Tang, and Xin Li contributed to the design of the clinical parts. Guoyou Qin and Wei Zhang helped with data analysis. Beini Fei wrote the manuscript.

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Competing interests statement

The authors declare that they have no competing interests.

Patient consent for publication

Not required.

Ethics approval

The study was approved by the Zhongshan Hospital Ethics Committee. (Approval No. B2019-274(2) R)

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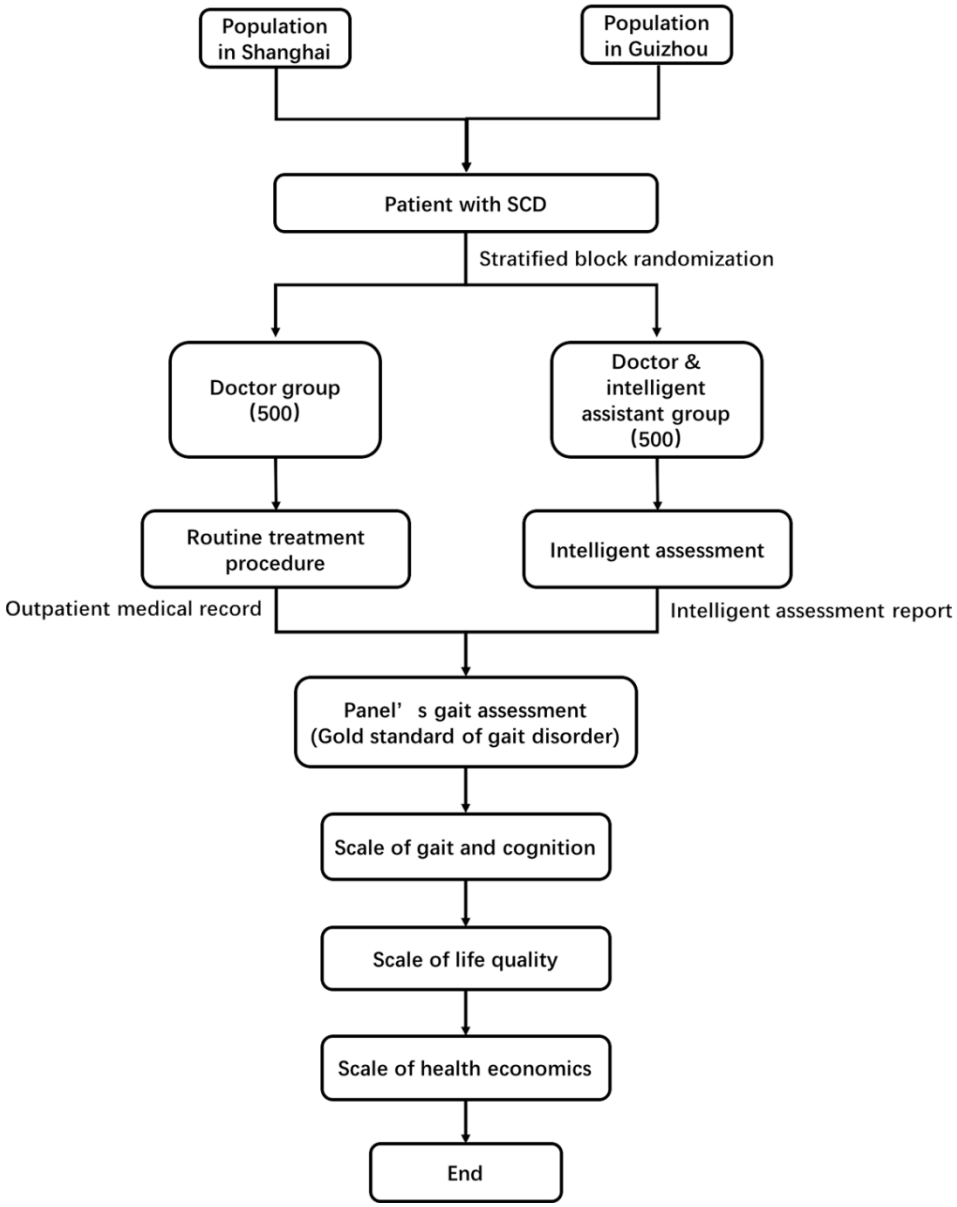
Figure legend

Figure 1 Flow diagram of ACCURATE-1.



Flow diagram of ACCURATE-1.

99x0mm (300 x 3001181 DPI)

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ABSTRACT

Introduction:

Silent cerebrovascular disease (SCD), which is a common disease in the elderly, leads to cognitive decline, gait disorders, depression, and urination dysfunction, and increases the risk of cerebrovascular events. Our study aims to compare the accuracy of the diagnosis of SCD-related gait disorders between the intelligent system and the clinician. Our team have developed an intelligent evaluation system for gait. This study will evaluate whether the intelligent system can help doctors make clinical decisions and predictions, which aids the early prevention and treatment of silent cerebrovascular diseases.

Methods and analysis:

This study is a multi-centered, prospective, randomized and controlled trial.

SCD subjects aged 60–85 years in Shanghai and Guizhou will be recruited continuously. All subjects will randomly be divided into a doctor with intelligence assistance group or a doctor group, at a 1:1 ratio. The doctor and intelligent assistant group will accept the intelligent system evaluation. The intelligent system obtains gait parameters by an RGB-depth camera and computer vision algorithm. The doctor group will accept the clinicians' routine treatment procedures. Meanwhile, all subjects will accept the panel's gait assessment and recognition rating scale as the gold standard. The primary outcome is the sensitivity of the intelligent system and clinicians to screen for gait disorders. The secondary outcomes include the healthcare costs and the incremental cost effectiveness ratio (ICER) of intelligent systems and clinicians to screen for gait disorders.

Ethics and dissemination:

Approval was granted by the Ethics Committee of Zhongshan Hospital affiliated with Fudan University on November 26, 2019. The approval number is B2019-027(2) R. All subjects will sign an informed consent form before enrollment. Serious adverse events will be reported to the main researchers and ethics committees. The subjects'

data will be kept strictly confidential. The results will be disseminated in peer-reviewed journals.

Trial Registration Number: NCT04457908

Key words:

Adult neurology, Stroke, Health economics

Article Summary

Strengths and limitations of this study

- Independent research and development of the intelligent gait evaluation system.
- Compare the accuracy of diagnosing SCD-related gait disorders between the intelligent system and clinicians.
- Evaluates the effectiveness and cost-effectiveness of the intelligent systems.
- Enroll subjects both in economically developed areas and underdeveloped areas.
- Follow-up will not be involved.

INTRODUCTION

Silent cerebrovascular disease (SCD) is very common in the elderly, and often incidentally found by cranial imaging[1]. It presents as a lacunar infarct, white matter hyperintensities (WMH), and microhemorrhages on imaging. However, patients do not have acute symptoms. Reports on the prevalence rate of SCD varies, mainly due to the selection of different sample populations. Furthermore. there is a lack of relevant studies for people under 45 years of age. Approximately 25% of those over 80 years of age have SCD[2]. Leary[3] et al. found that more than 11 million people in the United States were newly diagnosed with cerebral infarction or hemorrhage on imaging, but only 770,000 of them had clinical symptoms. SCD lacks the symptoms of an acute neurological impairment. Thus, it is often overlooked by patients and doctors. Nonetheless, it is also associated with chronic neurological impairments. Multiple studies showed that SCD can lead to cognitive decline, gait disorders, depression, and urination dysfunction, and increase the risk of future cerebrovascular events[4-6]. Debette[7] et al. assessed the incidence of stroke, dementia, and death in 2229 community patients (mean age 62±9 years), and found that SCD patients had increased risk of stroke (hazard rate [HR]: 2.84, 95% CI :1.32 to 6.10), and dementia (HR: 6.12, 95% CI :1.82-20.54), which were independent risk factors.

Stroke results in high medical costs. Shelby[8] et al. analyzed the hospitalization cost for patients with cerebrovascular events in 137 community hospitals. Patients with SAH had the highest cost ($23,777, n=1,124), followed by patients with intracerebral hemorrhage ($10,241, n=3,139), ischemic cerebral infarction ($5,837, n=18,740), and transient ischemic attack ($3,350, n=7,861). The length of stay was 11.5 days for intracerebral hemorrhage, 7.5 days for intracerebral hemorrhage, 5.9 days for ischemic cerebral infarction, and 3.4 days for transient ischemic attacks.

Early detection of subtle neurological impairment in SCD and standardized intervention can help improve patient prognosis and reduce costs. At present, the diagnosis of SCD mainly relies on the imaging and clinical expertise of doctors, which may be subjective and leads to misdiagnosis. Therefore, the use of an intelligent system for early quantitative evaluation of neurological damage in SCD can reduce the evaluation time and differences between individuals. It also consequently helps in the early prevention of SCD and guides diagnosis and treatment while reducing medical costs.

METHODS AND ANALYSIS

Study Design

ACCURATE-1 is a multicenter, prospective, superiority, randomized parallel trial. (Figure 1)

Subjects will be randomly divided into a doctor and intelligent assistant group, and a doctor group at a 1:1 ratio. The doctor and intelligent assistant group will accept the intelligent system evaluation, while the doctor group will accept the clinician's routine treatment procedures. Meanwhile, all subjects will accept the panel's gait assessment and cognitive scales as the gold standard.

Setting and timeline

The trial will be conducted in 14 hospitals in Shanghai and Guizhou, including secondary and tertiary hospitals. All staff members of the trial have been trained before the trial started. Recruitment of patients started at 25 September 2019. The trial was halted for more than a year due to the COVID-19 pandemic. Recruitment is ongoing now. The trial is scheduled to end in February 2022.

Participants

In this study, subjects with SCD aged 60 to 85 years in Shanghai and Guizhou will be recruited continuously. Subjects can refuse to participate or withdraw from the trial at any stage without discrimination or unfair treatment, and their treatment and rights will not be affected. All subjects that agree to attend our trial will sign an informed consent form. After recruitment, eligible subjects will be selected for the study according to the inclusion and exclusion criteria.

The inclusion criteria are as follows:

- Aged 60 years to 85 years.
- Diagnosed with SCD, according to the 2016 statement issued by the American Heart Association (AHA) and American Stroke Association (ASA):
    - No clear previous history of stroke.

- Cranial magnetic resonance imaging (MRI) shows at least one of the following finding within one year and Digital Imaging and Communications in Medicine (DICOM) data should be provided. 1) A lacunar infarct of vascular origin: subcortical round or ovoid fluid-rich lacunar lesion with a diameter of 3–15 mm, showing low central signal and irregular marginal high signal on T2-flair. The central signal is similar to the cerebrospinal fluid. Fazekas scores should be ≥2 points. 2) WMH of vascular origin: high signal on T2-flair in the white matter area (periventricular or subcortical). Fazekas scores should be ≥2 points. 3) Cerebral microbleeds: small, round, empty focus lesion on SWI or T2-weighted image, 2–10 mm in diameter. The number of microbleed lesions should be ≥5.

- Conscious and able to complete cognitive assessment.

- Able to stand and walk independently and complete gait assessment without assistance.

- Sign the informed consent.

The exclusion criteria are as follows:

- Intracranial lesions have been clearly diagnosed as a demyelination disease, leukodystrophy, intracranial space-occupying lesions, autoimmune encephalitis, etc.

- Previously be diagnosed as Parkinson's disease, normal pressure hydrocephalus, peripheral neuropathy, osteoarthritis.

- Previously be diagnosed as Alzheimer's disease, frontotemporal dementia, Lewy body dementia, etc.

- Severe neurological diseases such as previous cerebral trauma, epilepsy and myelopathy, etc.

- Cannot accomplish the cognitive assessment, such as severe visual or hearing impairment.

- Cannot finish the gait assessment, such as severe cardiovascular disorder.

Study procedure

Appropriate subjects will be selected based on the inclusion and exclusion criteria. Clinical data will be collected by doctors based on patients' demographics, medical history, neurological function assessment, laboratory examinations, imaging tests, quality of life, health service utilization, socioeconomic status, and medical and other social costs. The entire data collection process will be recorded only for data verification and monitoring.

Whether the subject's cranial MRI meets the inclusion criteria will first be determined by trained doctors according to the STRIVE standard. The committee of experts, including clinical radiology experts and image post-processing technology personnel, will review the DICOM data. Subjects who do not pass the review will be excluded accordingly.

Subjects in the doctor and intelligent assistant group will be tested for the Time Up and Go Test[9] (TUG) evaluated by the intelligent system. The accuracy of this system in screening abnormal gait performance is 90.14%[10]. The intelligent system contains an RGB-depth camera, using to record the TUG tests that include walking video, two-dimensional color images and scene depth images. The gait parameters in TUG test are obtained by computer vision algorithm and the data queue is established. The algorithm can track human motion in the video and identify the main joints in each frame to achieve pose estimation. Then, the previously extracted parameters are taken as input, and a machine learning-based classifier is used to filter abnormal gait.

Mini-Cog test[11] will be used to screen subjects' memory and executive function. Subjects will be asked to remember three unrelated words and immediately repeat these three words. Afterwards, they will be asked to draw a clock with 12 numbers and a pointer to 3:40, then recall the three words. Subjects will retell the sentences of the Mini-Mental State Examination[12] (MMSE) and the Montreal Cognitive Assessment[13] (MoCA). Subjects will be asked to repeat "44 stone lions," "I only

know Zhang Liang came to help today," and "The cat always hid under the sofa when the dog was in the room" in Chinese. The intelligent system will access the subjects' gait characteristics (get up, turnaround time, stride length, step velocity, stride length, step width, etc.), language features (pronunciation, intonation, word order, wrong language, language fluency, etc.), and clock features (circle, number, pointer).

Subjects in the doctor group will undergo routine medical procedures. There is only one doctor in the doctor group of each center. The doctor group is required to comprise of attending or resident physicians in neurology and/or attending/resident physicians receiving standardized training in neurology. The physician will register his/her professional qualifications, relevant knowledge training experience, educational background, and working years. The physician will determine whether the subjects have gait disorders through routine medical procedures such as their present and previous medical history and physical examination data.

The video of the TUG test of all subjects (including the doctor group and the doctor and intelligent assistant group) will be evaluated by two specialists in movement disorders as the gold standard. Specialists will be blinded to the group allocation. They will classify the subjects' gait as normal or abnormal. If the results are different, the opinion of the third expert will be included.

All subjects will be evaluated based on the following scales under the guidance of a trained doctor: 1) MMSE[12]: evaluates time and place orientation, immediate and delayed memory, attention and computation, naming, retelling, listening comprehension, reading and expression, and visual-spatial ability, with scores ranging from 0 to 30; 2) MoCA[13]: evaluates visual space, executive function, naming, memory, attention, language, abstraction, and orientation, scores ranging from 0 to 30; 3) Color Word Test[14] (CWT): evaluates semantic activation, dominant response inhibition, attention, working memory, information processing speed, etc.; 4) Digit Span Test[15] (DST): evaluates immediate memory and attention; 5) Verbal Fluency Test[16] (VFT): evaluates language capabilities; 6) TUG[9]: evaluates the total time subjects will take to complete it, with the average value obtained after three repetitions; 7) 10- Meter Walk Test[17] (10 MWT): The subjects will walk 10 m in a straight line at normal walking speed, while the time and number of steps required for

the subject to complete the 10 MWT will be recorded, with the average value obtained after three repetitions; 8) Tinetti Performance-Oriented Mobility Assessment[18] (TinettiPOMA): This includes balance and gait tests, with a maximum score of 28. A score between 19 and 24 indicates a risk of falling, while a score below 19 indicates a high risk of falling[19].

All subjects will be evaluated using the 5-level version of EuroQol Five Dimensions Questionnaire [20](EQ-5D-5L), which describes the health-related quality of life of the subjects.

Resources for health services are limited, especially in remote areas. It is important to evaluate the economics of our smart systems. Cost-effectiveness[21] is used to assess how much it costs that intelligent systems and doctors to diagnose each gait disorder. To evaluate the cost-effectiveness from the healthcare system and the societal perspectives, we will collect the data of unit costs and utilizations of the equipment, medications, and labor hours taken to deliver each individual diagnosis, as well as the additional cost of patients' accommodations, transportation, and productivity losses due to their disease. The labor hours taken will be collected through a questionnaire for staffs, while the equipment cost (intelligent system) will be amortized over its estimated lifespan. The medication and other patient costs will be collected using a patient questionnaire. (Table 1)

Table 1. Assessment of two groups.

Assessment	Doctor & intelligent assistant	Doctor
Intelligent TUG test	×	
Intelligent Mini-cog test	×	
Intelligent sentence repetition test	×	
Routine treatment procedure		×
Panel's gait assessment	×	×

TUG	×	×
10MWT	×	×
TinettiPOMA	×	×
MMSE	×	×
MoCA	×	×
CWT	×	×
DST	×	×
VFT	×	×
EQ-5D	×	×
Number of falls	×	×
Utilization and unit cost	×	×

× indicates that the assessment took place. TUG, time up and go test; Mini-Cog, Mini-Cognitive Assessment ;10 MWT, 10m walking test; TinettiPOMA, Tinetti performance-oriented mobility assessment; MMSE, Mini-Mental State Examination; MoCA, Montreal cognitive assessment; CWT, Color word test; DST, Digit span test; VFT, verbal fluency test.

Assessments

Outcome measures

The primary outcome is the sensitivity of the intelligent system and clinicians to screen for gait disorders.

The secondary outcomes are as follows: 1) the specificity and the Youden index[22](calculate as sensitivity plus specificity minus one) of the intelligent system and clinicians to screen for gait disorders; 2) the positive and negative predictive values of the intelligent system and clinicians at different levels to screen for gait disorders, and 3) healthcare costs of intelligent systems and clinicians to screen for gait disorders, and the incremental cost effectiveness ratio (ICER)[21] will be estimated by cost per additional true case detected using an intelligent system versus clinicians.

Sample size

This study is a 1:1 superiority trial. Referring to the preliminary study of gait disorder in SCD and our group, we expect that the sensitivity of doctors and intelligent assistants will be 85%, while the sensitivity of the doctor group will be 68%. The power is 1-β =80%, with a significance level of α=0.05. According to our calculations, there should be 94 positive cases evaluated by the gold standard in each group. The expected shedding rate is 6%; therefore, each group required 100 positive cases. Considering that the positive rate of gait disorder in the population is approximately 20%, a total of 1000 subjects should be included. NCSS Statistical Software 2021 was used to calculate sample size. (https://www.ncss.com/)

There are 14 sub-centers for the two regions in our study, including three secondary and three tertiary hospitals in Shanghai, and four secondary and four tertiary hospitals in Guizhou. The expected ratio of patients in secondary and tertiary hospitals is 1:2; in principle, no less than 30 subjects should be enrolled in each center, and 400 subjects for each region.

Randomization

Stratified blocked randomization will be used in this study. Stratification factors included regions (Shanghai and Guizhou), and hospital levels (secondary and tertiary hospitals). All subjects meeting the inclusion criteria are randomly divided into a doctor and intelligent assistant group and a doctor group at a 1:1 ratio through the central randomization system.

Data analysis

The normality was tested with the Shapiro–Wilk test. Continuous data with a normal distribution are expressed as the mean ± standard deviation. Data with non-normal distribution are presented as medians with interquartile ranges. A t-test or non-parametric test will be used to compare continuous data. Count data are expressed as frequency (%). For comparison of categorical variables, the chi-square test, Fisher's exact probability test, or Cochran–Mantel–Haenszel test will be used. Subgroup analyses will include region and hospital levels. An intention-to-treat analysis will be applied. Subjects who are randomly assigned to either the intelligent group or the doctor group will be analyzed as such, regardless of whether they received intelligent assessment or not. A significant difference was considered to be statistically significant

at $p < 0.05$. Statistical analyses were performed using the SAS 9.4.

A cost-effectiveness analysis will be conducted from a healthcare system and a societal perspective; all the costs and diagnostic outcomes will be listed separately, then the incremental cost will be calculated per true case additionally detected by using the intelligent system versus the clinicians. We will explore the possibilities of conducting a long-term cost-effectiveness analysis using economic decision modeling based on future cost savings and health gains by using the intelligent system versus clinicians to screen for gain disorder.

Patient and public involvement

Each patient will voluntarily participate in the study and sign the informed consent. Each subcenter will recruit patients according to the inclusion criteria and competed for enrollment. Patients will not involve in the design of this study. Patients don't need to assess the burden of the intervention. The result of this study will be disseminated via peer-reviewed journals.

DISCUSSION

Our study aims to compare the accuracy of the diagnosis of SCD-related gait disorders between the intelligent system and the clinician. Furthermore, we aim to evaluate the effectiveness and equity of intelligent systems to diagnose SCD-related gait disorders compared to clinicians.

Early identification of the characteristic gait of SCD is helpful for clinical diagnosis and treatment. Studies have found that the deterioration of neural gait disorder is often associated with impaired cognitive function, which can serve as a warning sign of dementia. Rosso[23] et al. reported that after a 14-year-follow-up, gait slowing was associated with cognitive impairment in the elderly population (OR per 0.1 s/y slowing 1.47; 95% CI, 1.04–2.07). After nine years of follow-up, Dumurgier[24] et al. found that 296 of the 3,663 subjects developed dementia, in which a decreased pace was associated with an increased risk of dementia, with a HR value reaching 3.39 for

every 0.007 m/s decrease in pace [95% CI 1.37-8.43]. Therefore, early quantitative gait analysis will help in the early detection of cognitive impairment. Appropriate interventions are needed to improve patient outcomes and prognoses.

However, the assessment of gait and cognitive function mostly depends on the visual or scale method used by doctors. Due to the lack of a unified evaluation process, the results are relatively random and inconsistent. Therefore, using artificial intelligence to detect gait disorder not only reduces time and labor costs, but also avoids individual evaluation differences. There were some researches based on intelligent gait analysis with wearable devices. Ahad et al[25] collected gait data using three sensors placed in a belt and backpack. They analyzed 67 solution and found that the best result achieved 24.23% prediction error for gender estimation, and 5.39 mean absolute error for age. Qiu et al[26] used inertial sensors to monitor the function of the body's lower limbs and capture their movements to reconstruct a three-dimensional model. Our intelligent system is easy to operate and has low requirements on hardware and site. Meanwhile, to the best of our knowledge, this is the first study to analyze gait features in SCD based on an intelligent system.

Currently, no studies have explored the effectiveness of SCD screening in reducing adverse health events or cost-effectiveness[1]. Although SCD may cause dementia and increase the incidence of stroke, the absolute risk is not high. Therefore, screening requires a low-cost and highly efficient test method. Artificial intelligence is a good choice. We will investigate the human, material, and financial costs of physicians and artificial intelligence in different regions when assessing a patient's neurological function. We hope that our intelligent system can reduce the cost of SCD screening and improve diagnosis in remote areas.

Ethics and dissemination

The subjects' rights will be protected according to the regulations of the China Food and Drug Administration, the Declaration of Helsinki, and the International Conference on Harmonization - Good Clinical Practice (ICH-GCP). The study was approved by the Zhongshan Hospital Ethics Committee. (Approval No. B2019-027(2)

R). The subjects' data will be kept strictly confidential. The results will be disseminated in peer-reviewed journals.

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Authors' contributions

Xin Wang, Jing Ding contributed to the conception and design of the study. Min Hu and Jin Zhao contributed to the design of the health economics part. Beini Fei, Yanmin Tang, and Xin Li contributed to the design of the clinical parts. Guoyou Qin and Wei Zhang helped with data analysis. Beini Fei wrote the manuscript.

Funding statement

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Competing interests statement

The authors declare that they have no competing interests.

Patient consent for publication

Not required.

Ethics approval

The study was approved by the Zhongshan Hospital Ethics Committee. (Approval No. B2019-027(2) R)

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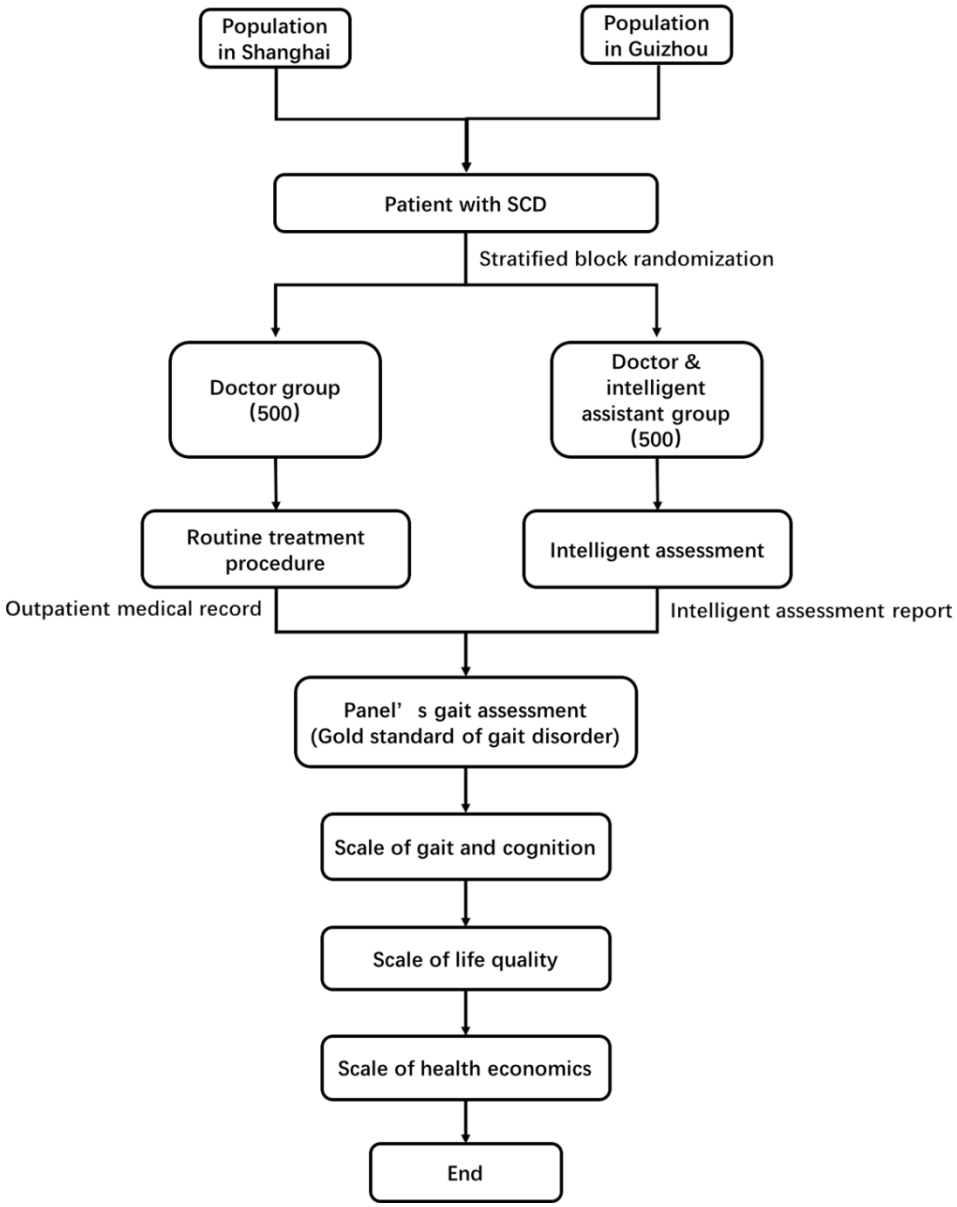
Figure legend

Figure 1 Flow diagram of ACCURATE-1.



Flow diagram of ACCURATE-1.

99x0mm (300 x 3001181 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Line/Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1/1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4/3
	2b	All items from the World Health Organization Trial Registration Data Set	26/2
Protocol version	3	Date and version identifier	-
Funding	4	Sources and types of financial, material, and other support	13/14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	20/1
	5b	Name and contact information for the trial sponsor	20/1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	20/1
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10/11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	2/4
	6b	Explanation for choice of comparators	19/4
Objectives	7	Specific objectives or hypotheses	26/4

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4/5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	11/5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	24/5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	4/7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	15/7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not Applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not Applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9/10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11/5
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	18/10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10/11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15/11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	19/11
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16/11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16/8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not Applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15/7
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Not Applicable
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	29/13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	22/11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	2/12

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	28/11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11/7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not Applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	27/2
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not Applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	25/2
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not Applicable
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	27/2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not Applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	29/13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17/14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	29/13

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Attachment (informed consent)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	29/13
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not Applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not Applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attachment
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not Applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.