Treatment with intravenous alteplase in ischaemic stroke patients with onset time between 4.5 and 24 hours (HOPE): protocol for a randomised, controlled, multicentre study

Zhongyu Luo,1 Ying Zhou,1 Yaode He,1 Shenqiang Yan,1 Zhicai Chen,1 Xuting Zhang,1 Yi Chen,2 Lu-Sha Tong,1 Wansi Zhong,1 Haitao Hu,1 Kemeng Zhang,1 Jiansheng Yang,1 Bruce C V Campbell,2 Min Lou

ABSTRACT

Background While intravenous thrombolysis is recommended for patients who had an acute ischaemic stroke (AIS) within 4.5 hours of symptom onset, there are few randomised trials investigating the benefits of thrombolysis beyond this therapeutic window.

Aim To determine whether patients who had an AIS selected with the presence of potentially salvageable tissue on CT perfusion at 4.5–24 hours after stroke onset (for stroke with unknown onset time, the midpoint of the time last known to be well and symptom recognition time; for wake-up stroke, the midpoint of the time last known to be well or sleep onset and wake up time) will benefit from intravenous thrombolysis.

Design HOPE is a prospective, multicentre, randomised, open-label blinded endpoint trial with the stage of phase III. The treatment allocation employs 1:1 randomisation. The treatment arm under investigation is alteplase with standard therapy, the control arm is standard therapy. Eligibility imaging criteria include ischaemic core volume ≤70 mL, penumbra ≥10 mL and mismatch ≥20%.

Study outcomes The primary outcome is non-disabled functional outcome (assessed as modified Rankin Scale score of 0–1 at 90 days).

Discussion HOPE is the first trial to investigate whether intravenous thrombolysis with alteplase offers benefits in patients who had an AIS presenting within 4.5–24 hours, which has the potential to extend time window and expand eligible population for intravenous thrombolysis therapy.

INTRODUCTION AND RATIONALE

Over the last decade, intravenous thrombolytic therapy has been the cornerstone treatment for patients who had an acute ischaemic stroke (AIS), which greatly improved clinical outcome and reduced mortality.1,2 In spite of the effectiveness and safety of intravenous thrombolysis (IVT), merely 5%–30% of patients who had an AIS are treated with IVT.3–5 The most recent American Heart Association/American Stroke Association (AHA/ASA) AIS guidelines recommend that patients who had an AIS should receive IVT within 4.5 hours from stroke onset.6 This short recommended therapeutic window for thrombolysis is one of the major reasons limiting the utilisation of IVT.

Fortunately, extending time window for reperfusion therapy by identification of salvageable tissue on imaging is feasible theoretically and practically. It has been reported that for patients with good collaterals, the time left for ischaemic tissue to be salvaged could last up to 42 hours.7 Other substantial evidences also suggested that potentially salvageable brain tissue might persist over 24 hours.8–9 Multiple randomised controlled trials (RCTs) have demonstrated that imaging-based selection of patients with extended time window to receive reperfusion therapy is safe and effective.10–13 The EXTEND trial11 and subsequent meta-analysis14 also provided strong evidence that selected patients with...
perfusion mismatch profile presenting within 4.5–9 hours from stroke onset still obtained overall net benefits from IVT. Perfusion mismatch criteria in these analyses included estimated ischaemic core volume <70 mL, ischaemic penumbra volume >10 mL and hypoperfusion/ischaemic core volume >1.2. Moreover, the therapeutic time window for endovascular recanalisation treatment has been expanded to 24 hours in 2018 AHA/ASA guidelines since the publication of DAWN and DEFUSE3. The secondary analysis of the DAWN study supported the clinical benefit of endovascular therapy in patients who had a stroke with witnessed onset (6–24 hours). Albers further analysed the data of HERMES, DAWN and DEFUSE3 trials, and found non-inferior treatment effects of late-window endovascular therapy compared with early-window therapy. The small core required in late-window trials and slow infarct growth might account for the benefits of reperfusion therapy in late-window studies. In addition, Wheeler et al also found that infarct continued to evolve for nearly 40 hours post onset in patients who had a stroke without reperfusion, suggesting possibility of rescuing viable tissue in late window. Furthermore, several studies have tried to expand the therapeutic window over 24 hours since the time last known to be normal. Thrombectomy was found to be associated with significantly higher odds of functional independence compared with medical management in patients presenting beyond 24 hours.

Also, the safety and functional outcomes of reperfusion therapy beyond 24 hours were comparable to reperfusion therapy between 6 and 24 hours. Thus, we can hypothesise that selection of patients using perfusion mismatch imaging profile may permit further extension of the therapeutic window for IVT.

Therefore, we presume that patients who had an AIS presenting with potentially salvageable tissue may benefit from IVT during the time window of 4.5–24 hours. Due to wide application of CT among distinct stroke centres, CT perfusion is chosen for evaluation of core and penumbra to select appropriate candidates for IVT in this study. Overall, this trial aims to investigate whether patients who had an AIS within 4.5–24 hours after symptom onset (for stroke with unknown onset time, the midpoint of the time last known to be well and symptom recognition time; for wake-up stroke, the midpoint of the time last known to be well or sleep onset and wake up time) can benefit from IVT if they meet the standard of CT perfusion screening (estimated ischaemic core volume ≤70 mL, ischaemic penumbra volume ≥10 mL and mismatch ≥20%).

**METHODS**

**Hypothesis**

Patients who had an AIS presenting within 4.5–24 hours after onset (for stroke with unknown onset time, the midpoint of the time last known to be well and symptom recognition time; for wake-up stroke, the midpoint of the time last known to be well or sleep onset and wake up time) with evidence of salvageable tissue might benefit from IVT.

**Design**

HOPE is a multicentre, prospective, randomised, open-label, blinded endpoint, phase III trial. Patients are randomised into treatment or control group with 1:1 proportion. The treatment arm under investigation is alteplase with standard therapy, the control arm is standard therapy. Patient flow is presented in figure 1. The first patient was recruited in June 2021.

**Participating centres and patient population**

To qualify for participation, centres should meet the following minimum criteria: (1) local tertiary hospitals, (2) capable of performing IVT and completes more than 30 IVTs for patients who had an AIS each year and (3) the interval time from door to needle is less than 60 min.

Patients presenting with clinical signs of AIS within 4.5–24 hours (for stroke with unknown onset, the midpoint of the time last known to be well and symptom recognition time; for wake-up stroke, the midpoint of the time last known to be well or sleep onset and wake up time) are enrolled. Eligibility imaging criteria include ischaemic core volume ≤70 mL, penumbra ≥10 mL and mismatch ≥20% (as evaluated by CT perfusion). For patients with major artery occlusion, the decision for endovascular treatment is made prior to randomisation.

![Figure 1](http://svn.bmj.com)  
Figure 1  Trial flow chart. CTP, CT perfusion; DWI, diffusion-weighted imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; R, randomisation; rt-PA, recombinant tissue plasminogen activator.
Patients who choose to receive endovascular therapy are excluded. Selection criteria (inclusion/exclusion criteria) are detailed in table 1.

### Randomisation
Patients are randomised and allocated to either treatment or control arm using a secure, web-based randomisation system. Randomisation will be stratified by centre. Study outcomes assessors are blinded to treatment assignment.

### Intervention
The study intervention is the administration of recombinant tissue plasminogen activator (0.9 mg/kg (maximum 90 mg), 10% of total dose bolus over 1 min, followed by an infusion of the remaining 90% over 60 min). Patients in both groups will be treated at acute stroke units (or intensive care unit based on individual patient circumstances) according to the latest Chinese guidelines for AIS management.

### Clinical and imaging evaluation
The schedule of assessments for this trial is described in table 2. Neurological functional deficits will be assessed by an experienced neurologist blinded to the radiographic findings and treatment allocation. At baseline, 1 day and 7 days, the National Institutes of Health Stroke Scale (NIHSS) score will be assessed. At 90 days, the modified Rankin Scale (mRS) assessment will be performed via structured telephone interview.

Patients will have CT perfusion performed at baseline. Hypoperfusion is determined as time to maximum >6 s, and core as relative cerebral blood flow <30%. Penumbral mismatch is the area subtracting core from hypoperfusion area. The volume of core and mismatch will be calculated automatically by the locally used perfusion analysis software, including Siemens workstation, GE workstation, RAPID, MIStar, F-Stroke and so on.

The presence of haemorrhagic transformation, parenchymal haemorrhage (PH) and symptomatic haemorrhagic transformation will be evaluated on diffusion-weighted imaging/CT according to the Heidelberg definition at 24 hours.

### Primary outcome
The primary outcome is non-disabled functional outcome assessed as mRS score of 0–1 at 90 days.

### Secondary outcomes
1. Independent recovery assessed as mRS score of 0–2 at 90 days.
2. Dependent but ambulatory recovery assessed as mRS score of 0–3 at 90 days.
3. Recovery assessed by categorical shift in mRS at 90 days.
4. The change of the NIHSS score from admission to 1 day.

---

**Table 1**: Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients presenting with clinical signs of AIS within 4.5–24 hours from symptom onset (for stroke with unknown time of onset, the midpoint of the time last known to be well and symptom recognition time; for wake-up stroke, the midpoint of sleep onset or the time last known to be well and wake up time).</td>
<td>1. Intracranial haemorrhage shown on CT.</td>
</tr>
<tr>
<td>2. Age over 18 years.</td>
<td>2. Large (more than one-third of the territory of MCA) region of clear hypodensity on CT scan.</td>
</tr>
<tr>
<td>3. NIHSS range from 4 to 26.</td>
<td>3. Prestroke mRS score of &gt;1.</td>
</tr>
<tr>
<td>4. Imaging inclusion criteria: ischaemic core volume ≤70 mL, penumbra ≥10 mL and mismatch ≥20% (as evaluated by CT perfusion).</td>
<td>4. Other contraindications for alteplase.*</td>
</tr>
<tr>
<td>5. Informed consent from patient, family member or legally responsible person depending on local ethics requirements.</td>
<td>5. Intend to undertake endovascular therapy.</td>
</tr>
<tr>
<td>6. A life expectancy of less than 3 months.</td>
<td>7. Any other condition that could significantly increase the risk of severe bleeding (such as haemolytic uraemic syndrome or thrombotic thrombocytopenic purpura). The judgement is left to the discretion of investigators.</td>
</tr>
</tbody>
</table>

*Other contraindications for alteplase is in accordance with the latest Chinese guidelines for AIS management (detailed in online supplemental materials).

AIS, acute ischaemic stroke; ICH, intracerebral haemorrhage; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.
Table 2 Schedule of assessments

<table>
<thead>
<tr>
<th>Study period</th>
<th>Randomisation</th>
<th>Postrandomisation</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time point</td>
<td>Baseline</td>
<td>24 hours</td>
<td>7 days</td>
</tr>
<tr>
<td>Informed consent form</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic data</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity and medical history</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vital signs</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine laboratory assessments*</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imaging</td>
<td>CTP</td>
<td>NCCT/DWI</td>
<td>NCCT/DWI</td>
</tr>
<tr>
<td>Adverse event assessment</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modified Rankin Scale</td>
<td>Pre-stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barthel Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EUROQOL 5D-5L</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Routine laboratory assessments include coagulation profile, complete blood count and clinical chemistry (glucose, lipid profile, electrolytes, urea).

CTP, CT perfusion; EUROQOL 5D-5L, EuroQoL 5-dimensions 5-level; DWI, diffusion-weighted imaging; NCCT, non-contrast CT; NIHSS, National Institutes of Health Stroke Scale.

5. The change of the NIHSS score from admission to 7 days.

Safety outcome
1. Symptomatic haemorrhagic transformation at 24 hours.
2. PH at 24 hours.
3. All-cause death at 90 days.

Data collection and management
Patient data for each individual are documented in the archived case record form (CRF) and enter into a web-based trial database. The data transfer between browser and database will use a secure and encrypted connection, and access to the database will be password protected. The monitor will check the CRF for completeness and consistency.

Data monitoring body
Trial progress and patient safety will be monitored by an independent data monitoring committee periodically. The committee will determine whether amendment or early termination is needed. If the exclusion criteria need to be modified, for example, the evolved indications for thrombectomy, we will make amendments and submit the revised protocol to the local human ethics committee.

Sample size estimates
The sample size was estimated according to the results of the previous observational cohort at the coordinating centre, which included patients presenting with clinical signs of AIS within 4.5–24 hours of stroke onset (with the same eligibility criteria as HOPE trial). Overall, 62 patients (34 receiving IVT, 28 receiving standard therapy) were included in the observational cohort. No significant difference was found in age, onset time and baseline NIHSS score between groups, and the proportion of mRS 0–1 at 90 days in the experimental group and the control group was 35% and 21%, respectively. Based on a 15% drop-out rate, 372 patients (186 in treatment and control groups, respectively) would be required to detect a significant treatment effect (two-sided, p=0.05) with 80% power.

Statistical analyses
The comparison of primary outcome was performed with intention-to-treat analysis. Using binary logistic regression model, the comparison of proportion of non-disabled functional outcome (assessed as mRS 0–1 at 90 days) will be performed between treatment and control groups after adjustment for age, baseline NIHSS score and time from stroke onset to randomisation. Both of the analyses adjusted for confounders and unadjusted will be carried out. Despite this, adjusted analysis is prespecified as the primary outcome analysis for HOPE trial. An ordinal analysis of the full range (0–6) of the mRS will be undertaken (merging categories 5 and 6) as secondary analysis. Other approaches for secondary outcomes analyses will be employed based on standard statistical principles for qualitative or quantitative variables as appropriate.
location of infarct (anterior infarct vs posterior infarct) will be evaluated in subgroup analyses. To explore the efficacy of patients with 'wake-up' stroke and those with unknown time of onset, we will conduct subgroup analyses. Considering the differences among various perfusion analysis software in distinct centres, core lab will reconstruct all perfusion images of the patients using a uniform software and perform a sensitivity analysis after excluding patients who do not fulfil the imaging criteria.

**DISCUSSION**

HOPE will address the question whether patients who had an AIS during the time window of 4.5–24 hours can benefit from IVT on condition that they meet standardised CT perfusion mismatch criteria indicating the presence of salvageable penumbra. Multiple studies have confirmed the benefits of reperfusion therapy in patients who had an AIS with a penumbral imaging pattern, including less infarct growth and more favourable clinical outcomes.9 10 17 Furthermore, among patients with early recanalisation, the absence of penumbral pattern was found to be a major factor related to poor outcome.23 Moreover, the progress of the penumbra into the infarct tissue is highly variable between individuals.9 There are many relevant factors including collaterals, metabolic disease and genetic factors.24–26 Thus, evaluation of core and penumbra using multimodal imaging offers precise information for individual patients, and selection based on imaging is likely to identify appropriate candidates for IVT.

Hitherto, HOPE trial is the first RCT to investigate the effectiveness and safety of thrombolytic therapy with intravenous alteplase in patients who had an AIS with onset time of 4.5–24 hours, which has the potential to extend time window and expand the eligible population for IVT. In addition, there is scarcely randomised clinical trial investigating reperfusion therapy for Asian population in extended therapeutic window (>4.5 hours). HOPE will add evidence to this end. Furthermore, the imaging techniques used in this trial are those routinely practised in a range of stroke centres, increasing the generalisability of the trial results.

**Summary and conclusions**

HOPE is a randomised, multicentre, open-label blinded endpoint, phase III trial, which aims to investigate the efficacy and safety of IVT in patients who had an AIS with onset time of 4.5–24 hours. This trial has the potential to extend the time window of IVT and promote thrombolysis utilisation.

**Contributors** ZL, YZ, and ML conceptualised and designed the initial protocol. SY, BCVC and ML amended the initial protocol. ZL and YZ drafted the manuscript. ZZ, XZ, YY, L-ST, WZ, HH, KZ and JY contributed to the acquisition of data. All authors have read and approved the final version of the manuscript to be published.

**Funding** HOPE is sponsored and supported by the Second Affiliated Hospital, School of Medicine, Zhejiang University.

**Competing interests** None declared.


SUPPLEMENTAL MATERIAL

Box 1. Inclusion and exclusion criteria

SPIRIT Checklist
**Box 1. Inclusion and exclusion criteria**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients presenting with clinical signs of AIS within 4.5 to 24 hours from symptom onset (for stroke with unknown time of onset, the midpoint of the time last known to be well and symptom recognition time; for wake-up stroke, the midpoint of sleep onset or the time last known to be well and wake up time).</td>
<td>1. Intracranial hemorrhage shown on CT.</td>
</tr>
<tr>
<td>2. Age over 18 years.</td>
<td>2. Large (more than one-third of the territory of MCA) region of clear hypodensity on CT scan.</td>
</tr>
<tr>
<td>3. NIHSS range from 4 to 26.</td>
<td>3. Pre-stroke mRS score of &gt; 1.</td>
</tr>
<tr>
<td>4. Imaging inclusion criteria: ischemic core volume ≤ 70 mL, penumbra ≥ 10 mL and mismatch ≥ 20% (as evaluated by CT perfusion).</td>
<td>4. Other contraindications for alteplase.a</td>
</tr>
<tr>
<td>5. Informed consent from patient, family member or legally responsible person depending on local ethics requirements.</td>
<td>5. Intend to undertake endovascular therapy.</td>
</tr>
<tr>
<td></td>
<td>6. A life expectancy of less than three months.</td>
</tr>
<tr>
<td></td>
<td>7. Any other condition that could significantly increase the risk of severe bleeding (such as hemolytic uremic syndrome or thrombotic thrombocytopenic purpura). The judgment is left to the discretion of investigators.</td>
</tr>
</tbody>
</table>

AIS, acute ischemic stroke; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; mRS, modified Rankin Scale.
Other contraindications for alteplase is in accordance with the latest Chinese guidelines for AIS management (detailed in supplementary materials), including: history of ICH; severe head trauma or stroke in the past 3 months; intracranial tumor or giant intracranial aneurysms; intracranial or spinal surgery within the last three months; major surgeries in the last two weeks; gastrointestinal or urinary system bleeding in the last 3 weeks; active internal hemorrhage; aortic arch dissection; arterial puncture in a site where hemostasis by compression is not easy to within the past week; elevation of blood pressure, systolic pressure $\geq 180$ mmHg or diastolic pressure $\geq 100$ mmHg; acute hemorrhagic tendency, including platelet count below $100 \times 10^9$/L or other conditions; receipt of low molecular weight heparin treatment within 24h; INR $> 1.7$ or PT $> 15$ s for patients who have taken anticoagulant orally; thrombin inhibitors or Xa factor inhibitors are being used within 48h, or the results of laboratory tests are abnormal (such as APTT, INR, platelet count, ECT; TT or appropriate Xa factor activity determination); blood glucose $< 2.8$ mmol/L or $> 22.22$ mmol/L.
SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*  

<table>
<thead>
<tr>
<th>Section/item</th>
<th>Item No</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative information</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym</td>
</tr>
<tr>
<td>Trial registration</td>
<td>2a</td>
<td>Trial identifier and registry name. If not yet registered, name of intended registry</td>
</tr>
<tr>
<td></td>
<td>2b</td>
<td>All items from the World Health Organization Trial Registration Data Set Please refer to Item 2a and registration at ClinicalTrial.gov (NCT04879615)</td>
</tr>
<tr>
<td>Protocol version</td>
<td>3</td>
<td>Date and version identifier</td>
</tr>
<tr>
<td>Funding</td>
<td>4</td>
<td>Sources and types of financial, material, and other support</td>
</tr>
<tr>
<td>Roles and responsibilities</td>
<td>5a</td>
<td>Names, affiliations, and roles of protocol contributors</td>
</tr>
<tr>
<td></td>
<td>5b</td>
<td>Name and contact information for the trial sponsor</td>
</tr>
<tr>
<td></td>
<td>5c</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>5d</td>
<td>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)</td>
</tr>
</tbody>
</table>

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 P5-P6

6b Explanation for choice of comparators P5-P6

Objectives 7 Specific objectives or hypotheses P6

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) P7

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 P7

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) P7

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered P7

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) P7-P8

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
"Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence" is not applicable because intervention (thrombolysis) is conducted during hospitalization.

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial P8
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>12</td>
</tr>
<tr>
<td>Participant timeline</td>
<td>13</td>
</tr>
<tr>
<td>Sample size</td>
<td>14</td>
</tr>
<tr>
<td>Recruitment</td>
<td>15</td>
</tr>
<tr>
<td>Methods: Assignment of</td>
<td></td>
</tr>
<tr>
<td>interventions (for controlled</td>
<td></td>
</tr>
<tr>
<td>trials)</td>
<td></td>
</tr>
<tr>
<td>Allocation:</td>
<td></td>
</tr>
<tr>
<td>Sequence generation</td>
<td>16a</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>16b</td>
</tr>
<tr>
<td>mechanism</td>
<td></td>
</tr>
<tr>
<td>Implementation</td>
<td>16c</td>
</tr>
<tr>
<td>Blinding (masking)</td>
<td>17a</td>
</tr>
</tbody>
</table>

**Outcomes**

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.

**Participant timeline**

Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure).

**Sample size**

Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations.

**Recruitment**

Strategies for achieving adequate participant enrolment to reach target sample size.

**Methods: Assignment of interventions (for controlled trials)**

**Allocation:**

- **Sequence generation**
  - 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.

- **Allocation concealment mechanism**
  - 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.

- **Implementation**
  - Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.

- **Blinding (masking)**
  - Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how.
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 P8-P9

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 P9

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 P9-P10

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 P10

20b  Methods for any additional analyses (eg, subgroup and adjusted analyses) P10

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) P10

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 P9
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
P9

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
P9

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
P9

**Ethics and dissemination**

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
P7

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)
P9

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
P13

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
P9-P10

Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site
P12

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
P9
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. Not applicable.

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. P9

31b  Authorship eligibility guidelines and any intended use of professional writers. P12

31c  Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code. P12

Appendices

Informed consent materials  32  Model consent form and other related documentation given to participants and authorised surrogates. Available from the corresponding author on reasonable request.

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. As routine data and there will be no biological specimens collected, this is 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.