

Alteplase for the treatment of acute ischemic stroke in patients with low National Institutes of Health Stroke Scale and not clearly disabling deficits (Potential of rtPA for Ischemic Strokes with Mild Symptoms PRISMS): Rationale and design

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Abstract

Rationale: Over half of acute ischemic stroke patients have a low National Institutes of Health Stroke Scale of 0–5 and up to two-thirds may not appear clearly disabled at presentation. The efficacy of intravenous alteplase for the latter group is not known.

Aim: Potential of rtPA for Ischemic Strokes with Mild Symptoms (PRISMS) was designed to evaluate the safety and efficacy of intravenous alteplase for the treatment of acute ischemic stroke with National Institutes of Health Stroke Scale 0–5 and without clearly disabling deficits.

Sample size estimates: A maximum of 948 subjects were required to test the superiority hypothesis with 80% power, according to a one-sided 0.025 level of significance.

Methods and design: PRISMS was a multicenter, randomized, double-blind, placebo-controlled phase 3b clinical trial. Patients were randomized to the active arm (intravenous alteplase standard dose of 0.9 mg/kg, up to a maximum of 90 mg, plus oral aspirin placebo) or the control arm (intravenous alteplase placebo plus active oral aspirin dose of 325 mg).

Study outcome: The primary efficacy endpoint was favorable functional outcome, defined as a modified Rankin Scale score 0 or 1 assessed at 90-day postrandomization.

Keywords

Acute stroke therapy, intervention, ischemic stroke, methodology, protocols, alteplase

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Introduction and rationale

Over half of all patients with acute ischemic stroke (AIS) have a low National Institutes of Health Stroke Scale (NIHSS) of 0–5 at presentation.^{1,2} Up to two-thirds of those with low NIHSS will have deficits that appear nondisabling at presentation, and therefore are considered “mild” (Khouri and Kleindorfer, 2012, Personal Communication of supplemental data regarding La Rosa et al.).^{3,4} However, prospective observational cohort studies report significant rates (29–32%)

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of 90-day disability (modified Rankin Scale (mRS) 2–6) in patients with mild stroke (Fischer and Mattle, 2010, Personal Communication of supplemental data regarding Fischer et al.).^{5,6}

Among AIS patients who arrive within 3 h of symptom onset, a substantial proportion (40%) are not treated with alteplase *primarily* due to mild deficits at the time of treatment decision.^{7–9} Treatment rates of AIS patients with low NIHSS have increased in recent years, raising the question of the optimal management of patients with low NIHSS and deficits that appear nondisabling.^{10,11}

Although alteplase is of established benefit for patients with low NIHSS scores associated with disabling deficits,¹² it is unknown whether alteplase is beneficial for patients with low NIHSS scores associated with potentially nondisabling deficits (including both patients with persistently nondisabling deficits since onset or due to improvement to a nondisabling state). Eight of the nine prior major trials (NINDS Parts 1/2, ECASS 1/2/3, Atlantis Parts A/B, and EPITHET) explicitly excluded varying subsets of patients with the mildest deficits, and the ninth (IST 3) permitted their enrollment if there was physician equipoise regarding benefit, but did not collect data regarding specific deficits and perceptions of level of disability at presentation, precluding subgroup analysis.^{13,22,23} Currently, national clinical recommendations reflect this absence of definitive evidence regarding thrombolytic therapy in patients with low NIHSS scores and nondisabling deficits, stating that

...treatment of patients with milder ischemic stroke symptoms that are judged as nondisabling may be considered. Treatment risks should be weighed against possible benefits; however, more study is needed to further

define the risk-to-benefit ratio. (Class IIb; Level of Evidence C)^{14,24}

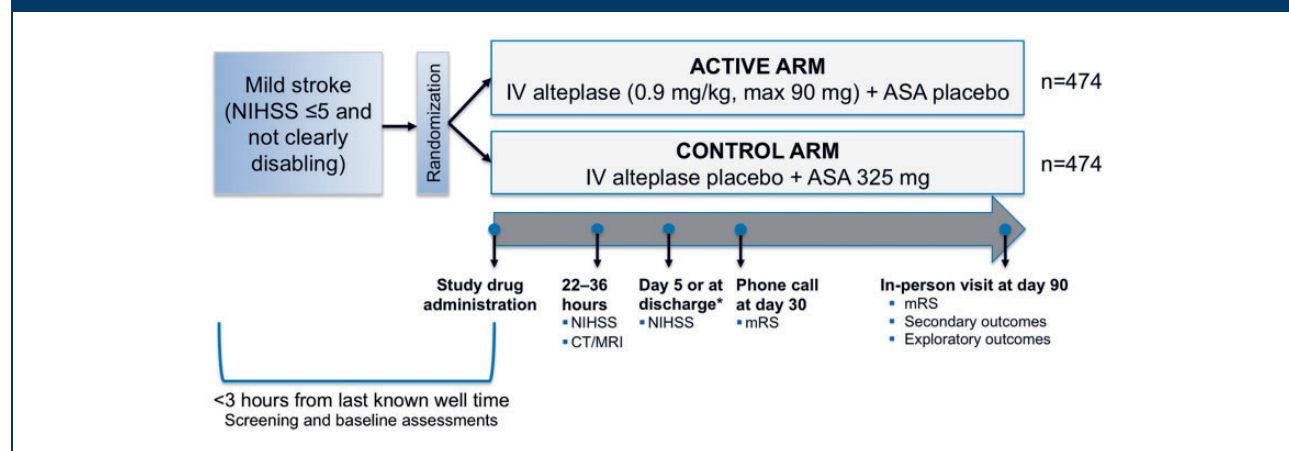
In designing the PRISMS trial, great consideration was given to the operational definition of stroke with low NIHSS and nondisabling symptoms. Eligibility based on an NIHSS threshold alone would capture some patients with clearly disabling symptoms. Drawing upon the work of a consensus panel,¹⁵ and seeking a clear, operationalized approach that accorded with the perspectives of patients, families, and physicians, the PRISMS Steering Committee defined PRISMS-eligible patients as those with NIHSS 0–5 and without “clearly disabling” deficits. Deficits were operationalized as “clearly disabling” if they would prevent return to employment or performance of basic activities of daily living at the time of the evaluation.

Methods

Design

PRISMS (NCT02072226) was designed as a phase 3b, multicenter, randomized, double-blind, placebo-controlled clinical trial intended to demonstrate the efficacy of intravenous (IV) alteplase for the treatment of mild AIS, as shown in Figure 1. Subjects were randomized to the active arm (IV alteplase standard dose of 0.9 mg/kg, up to a maximum of 90 mg, plus oral aspirin placebo) or the control arm (IV alteplase placebo plus active oral aspirin dose of 325 mg). The primary objective was to test the hypothesis that the active arm is superior to the control arm with respect to favorable functional outcome, defined as a mRS score of 0 or 1 at 90 days post randomization.

Figure 1. Study schema. ASA: aspirin; CT: computed tomography; IV: intravenous; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale.



Patient population

AIS patients with NIHSS 0–5 and deficits judged not clearly disabling by the investigator, and in whom study treatment could be initiated within 3 h of onset, were to be enrolled at approximately 75 sites in North America. Deficits were operationalized as “clearly disabling” if the current deficits were judged to prevent return to work or performance of basic activities of daily living (i.e. bathing, ambulating, toileting, hygiene, and eating). Sites were provided with pocket cards (Figure 2) describing the typically eligible patient.

Noteworthy exclusion criteria included functional disability prior to the enrolling stroke (defined as a historical mRS score of 2 or more). Subjects with an inability to swallow, preventing the administration of oral aspirin or aspirin placebo and suggesting a disabling deficit, were also ineligible. Full eligibility criteria are listed in Table 1.

Randomization and treatment

Given the known time dependence of any potential benefit from alteplase, in order to minimize time to study drug administration, eligible patients were randomized via a step-forward procedure.¹⁶ The step-forward procedure was designed to ensure that a randomized treatment assignment is available prior to the arrival of each eligible subject, so that treatment can be initiated as soon as possible. Subjects were randomized in a 1:1 ratio via a combination of the urn and biased coin methods, balanced within site.^{17–19}

As part of site activation, the interactive web response system (IWRS) assigned drug kit IDs for the first eligible subject at each site. Within 8 h of treatment initiation, the site was required to enter the corresponding patient data into the IWRS, in order to obtain and flag the drug kit ID to be used for the next eligible subject at that site. If potential subjects were deemed

Figure 2. Investigator pocket card to guide patient selection. NIHSS: National Institutes of Health Stroke Scale; PRISMS: Potential of rtPA for Ischemic Strokes with Mild Symptoms; RISS: rapidly improving stroke symptoms; TREAT: The Reexamining Acute Eligibility for Thrombolysis.

Protocol ML29093

A Proposed Definition of Mild Stroke/RISS (TREAT Task Force)

Improvement to a mild stroke (NIHSS ≤5), such that any remaining deficits appear non-disabling

As a guideline, the following should typically be considered disabling deficits:

- Complete hemianopsia (≥2 on the NIHSS “vision” question)
- Severe aphasia (≥2 on the NIHSS “best language” question)
- Severe hemi-inattention or extinction to more than one modality (≥ 2 on the NIHSS “extinction and inattention” question)
- Any weakness limiting sustained effort against gravity (≥ 2 on the NIHSS “motor” questions)

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†Further studies are warranted to explore these patient populations more
Levine SR et al. Stroke. 2013 July [Epub ahead of print];

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PRISMS Definition of Mild Stroke

NIHSS ≤5 and “Not Clearly Disabling”

- Consider the following...
 - Can patient still do basic ADLs and/or return to work?
 - >Basic ADLs: Dressing/bathing, Eating, Ambulating (walking), Toileting, Hygiene (“DEATH”)
 - Use TREAT Task Force definition of disabling as guideline

Examples of Typical PRISMS Patients
(But Always Consider Individual Patient Circumstances)

- Isolated mild aphasia (but still able to communicate meaningfully)
- Isolated facial droop
- Mild cortical hand, especially nondominant (NIHSS=0)
- Mild hemimotor loss
- Hemisensory loss
- Mild hemisensorimotor loss
- Mild hemiataxia (but can still ambulate)

Khatri, Pooja MD- 2014 (personal communication)

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Table 1. PRISMS eligibility criteria

Inclusion criteria
<ul style="list-style-type: none"> • Age 18 years (no upper limit) • Mild ischemic stroke = NIHSS ≤ 5 and not “clearly disabling” • Not “clearly disabling” = patient can still do basic ADLs and/or return to work • Study treatment can be started within 3 h from last known well time • Informed consent
Exclusion criteria
<ul style="list-style-type: none"> • CT or MRI findings consisting of one of the following: <ul style="list-style-type: none"> • CT with clear large hypodensity $> 1/3$ middle cerebral artery (MCA) territory or greater than 100 cc if not in MCA territory • MRI with clear large hyperintensity on concurrent DW and FLAIR $> 1/3$ MCA territory or greater than 100 cc if not in MCA territory • Imaging lesion consistent with acute hemorrhage of any degree • Evidence of intraparenchymal tumor • Disability (historical mRS score symbol for greater than or equal to 2) prior to the presenting stroke • Standard contraindications to IV alteplase for patients treated within 3 h of symptom onset, including: <ul style="list-style-type: none"> • Head trauma or previous stroke within the previous three months • Myocardial infarction within the previous three months • Gastrointestinal or urinary tract hemorrhage within the previous 21 days • Major surgery within the previous 14 days • Arterial puncture at a noncompressible site within the previous seven days • Any history of ICH with the exception of <5 chronic microbleeds on MRI • Elevated blood pressure (systolic > 185 mmHg or diastolic > 110 mm Hg), or the use of aggressive measures (use of more than two IV agents to lower blood pressure) to achieve blood pressure within acceptable parameters • Treatment with unfractionated heparin within the last 48 h and an activated partial thromboplastin time (aPTT) outside the normal range as specified by the center’s local laboratory • Blood glucose < 50 mg/dl • International normalized ratio (INR) > 1.7 (Note: This does not need to be verified prior to randomization if clinical abnormality is not suspected) • Platelet count of $< 100,000/\text{mm}^3$ (Note: This does not need to be verified prior to randomization if clinical abnormality is not suspected) • Treatment with a direct thrombin inhibitor or factor Xa inhibitor (e.g. dabigatran, rivaroxaban, apixaban, edoxaban) within the last 48 h • Treatment with a low-molecular-weight heparin (e.g. dalteparin, enoxaparin) within the last 48 h • Allergic reactions to study drug or aspirin • Inability to swallow, which would prevent oral intake of aspirin or aspirin placebo tablet • Other serious, advanced, or terminal illness that would confound the clinical outcome at 90 days • Current or recent (within three months) participation in another investigational drug treatment protocol • Anticipated inability to obtain three-month follow-up assessments • Previous enrollment in PRISMS • Any other condition that the investigator believes would pose a significant hazard to the patient if treatment with alteplase is initiated

CT: computed tomography; DW: diffusion-weighted; FLAIR: fluid-attenuated inversion recovery; ICH: intracranial hemorrhage; IV: intravenous; MRI: magnetic resonance imaging; mRS: modified Rankin Scale; NIHSS: National Institutes of Health Stroke Scale; PRISMS: Potential of rtPA for Ischemic Strokes with Mild Symptoms.

to meet prespecified eligibility criteria, the site pharmacist could premix study drug while informed consent was obtained. A subject was considered enrolled when the study drug bolus was administered. If the subject was not enrolled, the site was required to indicate in the IWRS that the corresponding drug kits were not used, and a new set of drug kit IDs was assigned.

Stroke mimic adjudication

Prior to database lock and unblinding, a subset of Steering Committee members reviewed the final diagnoses for all enrolled patients with either: (1) local site final diagnosis of neurovascular mimic, or (2) local site diagnosis of imaging-negative ischemic

stroke or transient ischemic attack (TIA). The central review group analyzed all relevant clinical records and data, blinded to treatment assignment. When central review group members had perspectives discordant with the local site final diagnosis, discussion was held between the site PI and central review group members. The site PI then made a final diagnostic determination.

Primary outcome – Efficacy

The primary endpoint was a mRS score of 0 or 1, reflecting favorable functional outcome, evaluated at 90 days post randomization.

Prespecified secondary and exploratory outcomes

The efficacy of IV alteplase was also evaluated by the full ordinal scale of the mRS and global favorable recovery using the Global Statistic (mRS 0 or 1, NIHSS 0 or 1, Barthel Index 95 or 100, and Glasgow Outcome Scale 1).²⁰

The primary safety endpoint was symptomatic intracranial hemorrhage (sICH) defined as any neurological decline attributed to ICH within 36 h, modified from the NINDS trials.²¹ Secondary safety outcomes include any ICH within 36 h, overall mortality within 90 days, and stroke-related and neurological deaths within 90 days.

Exploratory outcomes are listed in Table 2.

Safety monitoring

All adverse events (AEs), including serious AEs and nonserious AEs of special interest (AESIs), regardless of relationship to study drug, were reported until 30 days from study drug administration. After 30 days, the following events were captured: serious AEs, nonserious AESIs, and AEs resulting in withdrawal from study. AESIs consisted of sICH events (if not otherwise reported), stroke recurrence, or suspected transmission of an infectious agent via a medicinal product. Baseline laboratory, vital sign, neurological exam, and imaging data were collected to ensure that eligibility requirements were met. Follow-up (22–36 h) neuroimaging (MRI preferred if clinical standard of care) was required to assess for hemorrhage.

Data monitoring body

An independent Data Monitoring Committee (iDMC), composed of external advisors, provided ongoing review of accumulating safety data; the iDMC was also charged with review of the formal futility analysis,

planned to take place after 50% of subjects had completed follow-up.

Sample size determination

The PRISMS trial was designed to detect a 9% absolute difference in the proportion of subjects with favorable outcome with 80% power, using a one-sided type I error rate of 0.025 to test the superiority hypothesis, under the assumption that 65% of control subjects will experience a favorable outcome, and allowing for one interim futility analysis. It was anticipated that a higher rate of favorable outcome in controls would allow for more power to detect a lower treatment effect. The interim futility analysis was to be conducted according to an O'Brien–Fleming-type boundary, after 50% of the sample had completed the 90-day assessments. These assumptions resulted in a sample size of 856 subjects. Because the analysis would be conducted according to the ITT principle, the sample size was further adjusted to account for dilution of the treatment effect associated with 5% nonadherence (due to loss to follow-up, consent withdrawal, treatment crossovers, and neurovascular (stroke/TIA) mimics). The maximum sample size was therefore 948 subjects.

Statistical analysis

The PRISMS trial was designed to test the primary endpoint via a Cochran–Mantel–Haenszel test, stratified by age (<65 versus ≥ 65), time from onset to treatment (0–2 versus > 2 h), and pretreatment NIHSS score (0–2 versus 3–5).

Study organization and funding

The initial protocol was designed by the academic team and brought to Genentech, Inc. for consideration. After requested modifications, Genentech, Inc. sponsored the study, distributed study drug, and provided oversight of study management. A Steering Committee, composed of sponsor representatives and external scientific advisors, provided recommendations regarding study conduct and analysis throughout the trial recruitment phase through regularly scheduled in-person and teleconference meetings. The Steering Committee remained blinded to treatment arm during the subject recruitment and follow-up phases; after database lock and completion of prespecified analyses, the Steering Committee became unblinded and participated in the review and interpretation of study results. All imaging was interpreted by two independent blinded neuroradiologists at the central imaging core.

Table 2. Exploratory outcomes

Cognition	
Animal Naming Test	To test executive function
Digit symbol coding from WAIS III	To assess processing speed and executive function more generally
Hopkins Verbal Learning Test Revised (HVLT-R) 1, 2, 3	To assess learning and episodic memory
Boston Naming Test, 2nd Ed (15-item short form)	To test language, lexical retrieval, and semantic memory
Digit Span (Forward and Backward)	To assess visuospatial abilities
Benton Judgment of Line Orientation (JOLO)	To assess learning and episodic memory
Controlled Oral Word Association	To assess learning and episodic memory
OTHER	
Stroke Impact Scale-16 (SIS-16)	Potentially more sensitive to physical effects of mild stroke than modified Rankin Scale
Stroke Recurrence	Derived from adverse event monitoring
Six Minute Walk Test	To assess walking speed
EuroQol-5 Dimension questionnaire (EQ-5D)	To assess quality of life
Center for Epidemiological Studies Depression Scale (CES-D)	To assess for depressive symptoms

Discussion

The PRISMS trial was designed to definitively evaluate the efficacy of alteplase administered within 3 h of onset of ischemic stroke with NIHSS 0–5 and without clearly disabling deficits at presentation, as compared to aspirin, to improve functional outcomes at 90-day post-randomization. If positive, the trial would likely mandate the treatment of all AIS patients with an objective deficit, regardless of severity or level of disability, who are otherwise eligible for IV alteplase. If negative, it would minimize risk to patients for whom there would be no significant clinical benefit of this therapy.

This first trial in this understudied patient population presented some unique recruitment challenges including delays to ED presentation by the patient, delayed diagnosis of presenting event as stroke by clinicians, less frequent stroke team activation, and lack of clinical equipoise among some subinvestigators at sites who had routinely offered or not offered treatment to these patients. Efforts to increase recruitment included frequent site contact by the sponsor's Medical Science Liaisons, webinars by steering committee members, a brochure and slide presentation designed to introduce the trial to patients in a standardized manner, and a web-based interactive patient selection educational

tool. However, recruitment lagged behind target and, on 21 December 2016, after 313 subjects had been randomized, the sponsor terminated enrollment due to delayed recruitment timelines.

In light of the early termination, prior to database lock and unblinding of the study team, the statistical analysis plan was updated to focus on estimation of treatment effects and confidence intervals rather than hypothesis tests. It was prespecified that the risk difference would be obtained from a linear model with the binary mRS 0–1 outcome as the response, and treatment, age, time from last known well to treatment, and baseline NIHSS as covariates. Quadratic terms for the continuous covariates would be added to the model if the Wald p-value for the quadratic term is <0.1.

The PRISMS trial represents the first randomized controlled trial in this population of strokes with low NIHSS and without clearly disabling deficits. The results will contribute to our understanding of the benefit, in terms of functional, cognitive and behavioral outcomes, and risk associated with alteplase treatment in mild stroke patients.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: SD Yeatts reports personal fees from

Genentech for role as a member of the Steering Committee of the PRISMS Trial, during the conduct of the study. JP Broderick reports fees from Genentech to the Department of Neurology and Rehabilitation Medicine for his role as a member of the Steering Committee of the PRISMS Trial, during the conduct of the study. A Chatterjee reports personal fees from Genentech for role as a member of the Steering Committee of the PRISMS Trial, during the conduct of the study. EC Jauch reports personal fees from Genentech for role as a member of the Steering Committee of the PRISMS Trial, during the conduct of the study. SR Levine reports personal fees and non-financial support from Genentech for role as a member of the Steering Committee of the PRISMS Trial during the conduct of the study; grants from Genentech, from outside the submitted work. JG Romano reports personal fees from Genentech for role as a member of the Steering Committee of the PRISMS Trial, during the conduct of the study; grants from Genentech to the University of Miami to support his role as PI of the Mild and rapidly Improving Stroke Study. JL Saver served as an unpaid member of the Trial Steering Committee under a no-remuneration contract with Genentech, advising on the design and conduct of the PRISMS trial. Dr. Saver also served as an unpaid site investigator in the PRISMS trial, for which the University of California received payments on the basis of clinical trial contracts for the number of subjects enrolled. Outside of the submitted work, Dr. Saver reports receiving contracted hourly payments and travel reimbursement from Medtronic, Stryker, and Neuravi, and Boehringer Ingelheim (prevention only) for service on Trial Steering Committee(s), making recommendations regarding best approaches to rigorous trial design and conduct. The University of California has patent rights in retrieval devices for stroke. A Vagal reports grants from Genentech to University of Cincinnati, during the conduct of the study. B Purdon and J Devenport report being full time employees of Genentech. P Khatri reports payment to university department for research efforts from Genentech (lead PI of PRISMS), Neurospring (Co-investigator of CREATE grant), Lumosa (DSMB and consultant) and NIH/NINDS. She also reports fees from Biogen (DSMB), Medpace/Novartis (coinvestigator). She was an unpaid consultant to EmstopA and received travel support from Neuravi (academic workshop).

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References

1. Reeves M, Khoury J, Alwell K, et al. Distribution of national institutes of health stroke scale in the Cincinnati/Northern Kentucky stroke study. *Stroke* 2013; 44: 3211–3213.
2. Dhamoon MS, Moon YP, Paik MC, et al. Long-term functional recovery after first ischemic stroke. *Stroke* 2009; 40: 2805–2811.
3. Spokorny I, Raman R, Ernstrom K, et al. Defining mild stroke: outcomes analysis of treated and untreated mild stroke patients. *J Stroke Cerebrovasc Dis* 2015; 24: 1276–1281.
4. La Rosa FD, Khoury J, Kissela BM, et al. Eligibility for intravenous recombinant tissue-type plasminogen activator within a population. *Stroke* 2012; 43: 1591–1595.
5. Fischer U, Baumgartner A, Arnold M, et al. What is a minor stroke? *Stroke* 2010; 41: 661–666.
6. Khatri P, Conaway MR, Johnston KC, et al. Ninety day outcome of ischemic stroke with mild symptoms at presentation: ASAP study subanalysis. *Stroke* 2012; 43: 560–562.
7. George MG, Tong X, McGruder H, et al. Paul Coverdell National Acute Stroke Registry Surveillance – four states, 2005–2007. *MMWR Surveill Summ* 2009; 58: 1–23.
8. Smith EE, Fonarow GC, Reeves MJ, et al. Outcomes in mild or rapidly improving stroke not treated with intravenous recombinant tissue-type plasminogen activator: findings from get with the guidelines – stroke. *Stroke* 2011; 42: 3110–3115.
9. Messé SR, Khatri P, Reeves MJ, et al. Why are acute ischemic stroke patients not receiving IV tPA? Results from a national registry. *Neurology* 2016; 87: 1565–1574.
10. Asdaghi N, Romano JG, Wang K, et al. Abstract TP315: predictors of thrombolysis administration in patients with minor stroke or TIA in the Florida Puerto Rico collaboration to reduce stroke disparities (FL-PR CReSD) Study. *Stroke* 2016; 47 ATP315, originally published 16 February 2016.
11. Stecksén A, Asplund K, Appelros P, et al. Thrombolytic therapy rates and stroke severity. *Stroke* 2012; 43: 536–538.
12. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014; 384: 1929–1935.
13. Khatri P, Tayama D, Cohen G, et al. Effect of intravenous recombinant tissue-type plasminogen activator in patients with mild stroke in the third international stroke trial (IST-3): a post hoc analysis. *Stroke* 2015; 46: 2325–2327.
14. Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke. *Stroke* 2016; 47: 581–641.
15. Levine SR, Khatri P, Broderick JP, et al. Re-examining Acute Eligibility for Thrombolysis (TREAT) task force. Review, historical context, and clarifications of the NINDS rt-PA stroke trials exclusion criteria. *Stroke* 2013; 44: 2500–2505.
16. Zhao W, Mu Y, Tayama D and Yeatts SD. Comparison of statistical and operational properties of subject randomization procedures for large multicenter clinical trial treating medical emergencies. *Contemp Clin Trials* 2015; 41: 211–218.
17. Zhao W and Weng Y. Block urn design – a new randomization algorithm for sequential trials with two or more treatments and balanced or unbalanced allocation. *Contemp Clin Trials* 2011; 32: 953–961.

18. Wei LJ. The adaptive biased coin design for sequential experiments. *Ann Stat* 1978; 6: 92–100.
19. Efron B. Forcing sequential experiments to be balanced. *Biometrika* 1971; 58: 403–417.
20. Tilley BC, Marler J, Geller NL, et al. Use of a global test for multiple outcomes in stroke trials with application to the National Institute of Neurological Disorders and Stroke t-PA Stroke Trial. *Stroke* 1996; 27: 2136–2142.
21. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; 333: 1581–1587.
22. Khatri P, Kleindorfer DO, Yeatts SD, et al. Strokes with minor symptoms: an exploratory analysis of the NINDS rt-PA trials. *Stroke* 2010; 41: 2581–2586.
23. Sandercock P, Wardlaw JM, Lindley RI, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet* 2012; 379: 2352–2363.
24. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke. *Stroke* 2013; 44: 870–947.