Effect of waivers of consent on recruitment in acute stroke trials

A systematic review

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ABSTRACT

There is urgent need for clinical trials of novel interventions to reduce the burden of acute ischemic stroke. A key impediment to such trials is slow recruitment. Since obtaining written informed consent in the setting of acute stroke is especially challenging, some experts have endorsed relaxing the requirement for informed consent by permitting verbal consent or waivers to facilitate recruitment. This systematic review of 36 randomized controlled trials of acute interventions for ischemic stroke assesses whether alternatives to written informed consent are associated with increased recruitment rates. After the exclusion of 2 outlier trials that differed from other trials in conduct and interventions studied, no association was observed on univariable analysis (8.9 participants/month in trials requiring written consent vs 6.1 participants/month in trials with alternatives, $p = 0.43$) or multivariable analysis (when adjusting for the number of centers, number of countries, and exclusions based on modified Rankin Scale scores). Alternatives to written informed consent in acute stroke trials may enable trial designs that would not be feasible otherwise. However, we did not find evidence that, within traditional trial designs, such alternatives are associated with faster recruitment. *Neurology*® 2016;86:1543-1551

GLOSSARY

EFIC = Exception from Informed Consent; **HASTA** = Hyper Acute Stroke Alarm Study; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **PHANTOM-S** = The Pre-Hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke Patients Study; **PRISMA** = Preferred Reporting Items for Systematic Reviews and Meta-Analysis; **tPA** = tissue plasminogen activator.

Despite sweeping advances in stroke prevention and treatment including cardiovascular risk modification, acute reperfusion therapies, extensive public education, the establishment of stroke centers and systems of care, and new technologies such as telemedicine and imaging-based patient selection for endovascular treatment, ischemic stroke remains a leading cause of major disability and death. In recognition of the continuing need to improve outcomes in acute ischemic stroke, the NIH recently established a network of more than 200 sites (NIH StrokeNet) to provide infrastructure for stroke clinical trials.¹ However, one of the enduring challenges for most clinical trials (particularly for acute stroke trials) is slow recruitment, which poses a serious threat to feasibility and statistical power.^{2,3}

The requirement for informed consent has been described as the rate-limiting step of acute stroke trials.⁴ Obtaining informed consent for research poses numerous challenges for stroke clinical investigators. The stroke itself may render a patient aphasic or cognitively incapacitated. Multiple studies indicate that surrogate decision-makers, if available, are less willing to enroll incapacitated relatives in clinical research compared to when patients are given the option directly.⁵⁻⁷ The time window for intervention is narrow, which requires investigators to hastily obtain consent while preparing to deliver sometimes complex treatments. Recent trials testing hyperacute field-based interventions such as thrombolysis on mobile stroke units equipped with CT scanners have further narrowed the time window to obtain consent.^{8,9} Finally, many established and investigational therapies involve a complex weighing of risks and benefits, such that many people would choose to forego intervention if asked prospectively.^{10,11}

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Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram

Given these potential barriers to participant recruitment and the feasible conduct of scientifically rigorous trials, some experts have endorsed relaxing the requirement of informed consent through waivers to permit enrollment without consent. This suggests an ethical tension between respecting the rights of individual participants through stringent requirements of consent and pursuing wider societal benefit through more permissive requirements to facilitate acute stroke research. Existing empirical findings to guide this debate are limited. Secondary analyses of 2 large stroke trials indicate that most patients in those trials were enrolled via surrogate consent and that limiting trials to patients able to consent for themselves would have restricted the generalizability of these studies by excluding patients with more severe strokes.^{12,13} It is unclear whether other alternatives to written informed

consent, such as waivers or verbal consent, would also materially affect the feasibility and generalizability of acute stroke trials. We conducted a systematic review of acute stroke trials to assess whether the specific methods of obtaining informed consent are associated with the participant recruitment rate in these trials.

METHODS Trial identification. This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement and was registered at the International Prospective Register of Systematic Reviews (PROSPERO) in 2014 (CRD42014010204).

We searched Medline, PubMed, the Cochrane Database of Research in Stroke (DORIS), and the Stroke Trials Registry for English-language publications between January 1, 2010, and May 31, 2014, reporting the results of randomized controlled trials of acute interventions for ischemic stroke. The following text and MeSH terms were used in our search: Medline: stroke [MeSH terms] and (acute or endovascular procedures or thrombolytic therapy or tPA or plasminogen activator or fibrinolysis* or thrombectomy or reperfusion or recanalization); PubMed: (acute stroke or acute ischemic stroke or stroke and [endovascular procedures or thrombolytic therapy or tPA or plasminogen activator or fibrinolysis* or thrombectomy or reperfusion or recanalization] and [randomiz* or controlled] not Medline); DORIS: acute ischemic stroke with limiter acute treatment (<30 days) and filters RCTs and existing evidence; Stroke Trials Registry: acute ischemic for which the primary purpose was treatment with the filter completed studies. These searches yielded 871 articles, 135 of which were duplicates, giving a total of 736 unique articles (figure 1, adapted from PRISMA guidelines).

Screening. Articles met our inclusion criteria if they were randomized controlled trials evaluating acute interventions for ischemic stroke in individuals 18 years of age or older that were applied within 12 hours after symptom onset or up to 12 hours after symptom recognition for wake-up stroke. We excluded conference abstracts, dissertation abstracts, book chapters, reviews, and meta-analyses.

Two independent reviewers (W.B.F. and W.C.) screened the articles for inclusion. Reviewer 1 (W.B.F.) screened the titles and abstracts of all 736 articles (consulting full text in 31.7% of cases for further information). Reviewer 2 (W.C.) screened the first 50 articles and every 10th article thereafter. Among the articles screened by both reviewers, there was one disagreement about inclusion (agreement rate of 99.2%), which was resolved by discussion and consultation with a third reviewer (A.S.K.). The search yielded 36 trials (61 articles) after removing 14 trials with published primary outcomes before 2010 and 10 trials with published protocols that had not yet been completed.

Data extraction. We extracted the following data for the 36 trials: number of participants, trial duration, number of centers, countries, interventions, individual vs cluster randomization, whether the primary outcome was clinical efficacy, range of permitted NIH Stroke Scale (NIHSS) scores, presence of exclusion criteria based upon decreased consciousness, range of permitted modified Rankin Scale (mRS) scores, maximum permissible time from symptom onset to study randomization, mean time from symptom onset to study randomization, whether consent was sought, whether consent was required, justification provided if consent was not required, number of individuals who refused

consent, whether consent occurred before or after hospital arrival, written vs verbal consent, surrogate vs direct consent, rejection of the null hypothesis, and journal where primary outcome data were published.

Where information about a trial could not be located in the articles from our search, we consulted other publications, including published protocols and clinicaltrials.gov. We also e-mailed trial investigators directly for further information (all but one responded to our requests).

Statistical analysis. Before conducting our analysis, we identified potential outliers based upon visual examination of scatterplots of recruitment rate against other study parameters such as the number of centers, maximum time to randomization, and types of intervention studied. We then scrutinized the methods and interventions in these trials for qualitative differences that might indicate that recruitment was not subject to the same constraints as in the remainder of the dataset. Multivariable modeling of predictors of recruitment rate was performed by stepwise forward linear regression, and variables were retained in the model if $p < 0.2$. Stepwise addition of variables was undertaken in the following order based upon a priori assumptions: location

of intervention (prehospital or hospital), number of centers, number of countries, form of consent, maximum time to randomization, endovascular trial, thrombolytic trial, region, and presence of exclusionary criteria (NIHSS, mRS, consciousness). Analysis was performed using Stata 13.1 (StataCorp, College Station, TX); a 2-tailed p value of <0.05 was considered significant. All means were unweighted.

Post hoc evaluation of second-generation endovascular trials. Following completion of our prespecified search for this review, data from 5 high-profile second-generation endovascular trials were published, which all demonstrated benefit of mechanical thrombectomy.^{14–18} Since these trials were not captured by our prespecified protocol, they were not included in the primary analysis. However, we repeated our analysis after including these new trials in order to test how robust our original findings were in the setting of these new data.

RESULTS A total of 36 trials with 17,793 patients met our criteria for inclusion (table 1).^{8,9,19–52} None of the 36 trials that required informed consent barred

Table 1 Comparison of trials by informed consent requirements

	Written consent required	Written consent not required	p Value
No. of trials, total	26	9	
No. of patients, total	6,672	10,975	
No. of patients per trial, mean (SD)	256.6 (283.4)	1,219.4 (2,095.3)	0.25
Trial region, n (%)			0.13
North America	6 (23.1)	0 (0)	
Europe	10 (38.5)	8 (88.9)	
Asia	4 (15.4)	0 (0)	
Australia	1 (3.8)	0 (0)	
Multiple	5 (19.2)	1 (11.1)	
No. of countries per trial, mean (SD)	2.5 (3.6)	2.7 (3.7)	0.91
No. of centers per trial, mean (SD)	25.4 (36.9)	26.1 (49.8)	0.96
Intervention, n (%)			0.41
Antithrombotic	3 (11.5)	0 (0)	
Thrombolysis	2 (7.7)	3 (33.3)	
Endovascular	5 (19.2)	1 (19.1)	
Neuroprotectant	14 (53.8)	4 (44.4)	
Other	2 (7.7)	1 (11.1)	
Location, n (%)			<0.01
Hospital	25 (96.2)	4 (44.4)	
Prehospital	1 (3.8)	5 (55.6)	
Maximum time to randomization, h, mean (SD)	6.4 (2.8) (n = 26 trials) (n = 6,672 patients)	4.4 (1.3) (n = 9 trials) (n = 10,975 patients)	>0.05
Trial duration, mo, mean (SD)	35.4 (20.2) (n = 25 trials) (n = 6,632 patients)	40.8 (38.1) (n = 9 trials) (n = 10,975 patients)	0.59
Recruitment rate, participants/mo, mean (SD)	8.9 (8.4) (n = 25 trials) (n = 6,632 patients)	52.4 (100.4) (n = 9 trials) (n = 10,975 patients)	0.03
Rejected null hypothesis (efficacy trials), n (%)	4 of 20 trials (20.0)	3 of 6 trials (50.0)	0.29
Primary publication impact factor, mean (SD)	16.1 (18.4)	19.3 (18.7)	0.66

surrogate consent, and all but 8 explicitly permitted it. Written informed consent was required prior to randomization in 26 of these trials and was not required prior to randomization in 9 trials. (Information about the form of consent was not available for one trial.⁵²) Among the 9 trials that did not require written consent, 7 of these sought consent but permitted waivers,^{8,9,26,31,32,40,46} one did not seek consent at all,²⁸ and one permitted verbal consent.³⁷

Refusals of consent. Data on individual refusals of consent were available for 15 trials (41.7%), either from published literature or provided upon request by investigators. In 3 trials (8.3%), failures of consent were reported, but refusals were not distinguished from other causes of an inability to obtain consent.^{44,45,51} Twelve trials (33.3%) did not log refusals, confirming this decision in direct correspondence. Five trials (16.7%) did not provide information about the availability of such data, even after specific requests. One trial (2.8%) did not seek consent.²⁸ The refusal rate—defined as the number of individuals who refused

consent over the number of potential consenters (those who consented plus those who refused)—was 11.2% in the 15 trials with data (3,435 consents; 433 refusals; 3,868 potential consenters).

Trials in which written informed consent was not required prior to randomization were identified. The 9 trials that did not require written informed consent prior to randomization (table 2) presented several rationales for using alternatives to written informed consent, including the permissibility of deferring consent,^{8,26} approval by an Ethics Board,^{28,32,46} the need for maximally rapid treatment,^{31,37} the right of patients not to have tissue plasminogen activator (tPA) withheld,⁹ and the ability of medical professionals to provide proxy consent.⁴⁰ One trial that, for the sake of analysis, was not grouped with the 9 trials that permitted waivers of consent required written informed consent at all 22 study sites except one, which was exempted “by the FDA and the institutional review board.”³⁵

Many of these trials required later actions by patients to confirm consent. Patients in Combined

Table 2 Trials that did not require written consent

Trial name	Continent	Location	Intervention	Language of consent
PHANTOM-S ⁹	Europe	Prehospital	tPA on mobile stroke unit vs tPA in the hospital	“In accordance with ethics approval and standard in-hospital routine, we did not withhold tPA from patients who could not communicate because of coma or severe dysphasia (waived consent).”
HASTA ²⁸	Europe	Prehospital	Priority level 1 vs standard priority level	“The study was approved from the Regional Ethical Review Board... without need of consent from the participating patients.”
CERE-LYSE ²⁶	Europe	Hospital	Alteplase plus cerebrolysin vs alteplase plus placebo	“Patients who are incapable of giving consent may be included... These patients have to sign a written consent as soon as they are able to understand the meaning of the study and are able to sign.” (Cited in personal e-mail correspondence.)
INSULINFARCT ³¹	Europe	Hospital	Intensive insulin therapy vs usual subcutaneous insulin therapy	“Consent was not immediately required if the patient had severe language disturbances, neglect, or loss of consciousness so that the insulin treatment could be initiated as soon as possible.”
IST-3 ³²	Multiple	Hospital	tPA within 6 hours vs standard care (no tPA after 4.5 hours)	“... If no relative is available, some local ethics committees may permit a professional legal representative, such as an independent doctor, to enable those patients unable to give consent to be recruited.” (Cited in published protocol for the trial. ⁶⁰)
PIL-FAST ³⁷	Europe	Prehospital	Lisinopril in ambulance vs placebo in ambulance	“The patient is then asked to provide verbal confirmation that they are happy to take part. The consent process takes approximately three to five minutes. A longer consent process would delay transfer to the hospital.”
RIGHT ⁴⁰	Europe	Prehospital	Transdermal glyceryl trinitrate (TGN) in ambulance vs no TGN	“If the patient was unable to provide consent and there was no relative present, paramedics randomized patients into the trial after signing a proxy consent form on behalf of patients for the first part of the trial as witnessed by a second paramedic or ambulance technician.”
SYNTHESIS-Expansion ⁴⁶	Europe	Hospital	Endovascular therapy vs tPA	“If the patient is unable to provide a written consent, the center coordinator should seek guidance from its ethics committee... If no relatives are available, exemption from informed consent can be obtained by following the guidelines of the U.S. Food and Drug Administration and the Department of Health and Human Services that allows hospitals to proceed without informed consent in critical situations of emergency.” (Cited in protocol hyperlinked in primary article.)
Walter et al. ⁸ (2012)	Europe	Prehospital	tPA on mobile stroke unit vs tPA in the hospital	“... Written informed consent will be obtained from each participant (or the participant’s legally accepted representative) or deferred in exceptional circumstances according to the regulatory and legal requirements.”

Abbreviations: CERE-LYSE = Combined Treatment With Alteplase (Rt-PA) and Cerebrolysin® in Acute Ischemic Hemispheric Stroke; HASTA = Hyper Acute Stroke Alarm Study; INSULINFARCT = Efficacy and Safety of Continuous Intravenous Versus Usual Subcutaneous Insulin in Acute Ischemic Stroke; IST-3 = third International Stroke Trial; PHANTOM-S = The Pre-Hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke Patients Study; PIL-FAST = Paramedic Initiated Lisinopril For Acute Stroke Treatment; RIGHT = Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial; SYNTHESIS = Local Versus Systemic Thrombolysis for Acute Ischemic Stroke; tPA = tissue plasminogen activator.

Treatment With Alteplase (Rt-PA) and Cerebrolysin® in Acute Ischemic Hemispheric Stroke (CERE-LYSE) and Paramedic Initiated Lisinopril For Acute Stroke Treatment (PIL-FAST) had to provide subsequent written informed consent for inclusion in the trial.^{26,37} In The Pre-Hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke Patients Study (PHANTOM-S), only deidentified data could be gathered from individuals unable to give informed consent; later telephone follow-up at 3 months required written informed consent, as mandated under German law.⁹ In the Rapid Intervention with Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT), written informed consent was required by the patient or proxy at the hospital, after the first treatment dose had been given in the ambulance.⁴⁰ Efficacy and Safety of Continuous Intravenous Versus Usual Subcutaneous Insulin in Acute Ischemic Stroke (INSULINFARCT) stipulates that “consent was not immediately required” and Walter et al.⁸ alludes to “deferments,” though neither specifies later steps required for full inclusion.³¹

Outlier detection. Two potential outlier trials were identified (figure 2). PHANTOM-S was conducted over 21 months and had the largest number of enrolled participants (6,182 individuals) among the trials in this review, for a recruitment rate of 294.4 participants per month. The Hyper Acute Stroke

Alarm Study (HASTA) was conducted over 7 months and had the fourth largest number of enrolled participants (942 individuals), for a recruitment rate of 134.4 participants per month.

Closer examination revealed important differences in the conduct and interventions studied in these 2 trials, as compared with other studies in our review. PHANTOM-S was a cluster-randomized study of thrombolysis in a mobile stroke unit in which patients were allocated to interventions according to the week in which their stroke occurred; during control weeks, an ordinary ambulance was dispatched to bring patients to a hospital for workup and treatment, while during intervention weeks, a mobile stroke unit with on-board imaging and thrombolysis capabilities was dispatched. In HASTA, the intervention studied was the prehospital priority level assigned to stroke cases at the emergency dispatch center; patients with stroke symptoms were randomized at an individual level to standard priority or a higher priority for ambulance dispatch.

In both cases, allocation to the intervention group occurred prior to ambulance dispatch and thus prior to any clinical evaluation of the patient. Furthermore, neither trial tested clinical therapies (in both arms of these trials, patients were given thrombolysis whenever feasible) but instead tested systems-level interventions that influenced the speed and efficiency with which standard clinical treatments were delivered. We judged that the markedly faster recruitment rates achieved in these trials likely reflected that recruitment was not subject to many of the non-consent-related constraints in the remainder of trials, and therefore we excluded them from our main univariable and multivariable comparisons.

Recruitment rate of trials in which written informed consent was not required prior to randomization. On univariable analysis (of the entire dataset, including these 2 outlier trials), we found that trials of prehospital interventions were less likely to require written informed consent ($p < 0.01$). The prehospital interventions included 2 German trials of mobile stroke units with on-board imaging and thrombolysis capabilities (the only 2 cluster-randomized trials in this review),^{8,9} a Swedish trial in which participants in the intervention arm were assigned a higher prehospital priority level by the emergency dispatch center,²⁸ and 3 trials with paramedic-initiated therapies: lisinopril (UK),³⁷ ischemic preconditioning (Finland),³⁹ and glycerol trinitrate (UK).⁴⁰ Of these prehospital trials, only one required written informed consent en route to the hospital.³⁹

When the 2 outlier trials were included in analysis (see above), the mean recruitment rate of trials that did not require written consent was nearly 6 times the rate of trials that required it ($p = 0.03$). However,

Figure 2 Recruitment rate by maximum time to randomization

Markers for individual trials are scaled by the number of participants enrolled. HASTA = Hyper Acute Stroke Alarm Study; PHANTOM-S = The Pre-Hospital Acute Neurological Therapy and Optimization of Medical Care in Stroke Patients Study.

after removing these outliers, the mean recruitment rate of trials that did not require written consent was 6.1 participants per month (from 52.4 participants per month), compared to a recruitment rate of 8.9 participants per month in trials that required written consent ($p = 0.43$).

Multivariable predictors of recruitment rate. When outliers were included in multivariable analysis, the predictors of recruitment rate were prehospital location (regression coefficient [β] = 59.4, $p = 0.01$) and thrombolytic intervention (β 36.9, $p = 0.12$). When the outliers were excluded from multivariable analysis, the predictors of recruitment rate were the number of centers (β 0.25, $p < 0.001$), the number of countries (β -1.43, $p = 0.04$), and the use of exclusions based upon mRS criteria (β 3.73, $p = 0.08$).

Post hoc analysis including second-generation endovascular trials. When 5 second-generation endovascular trials (figure 3) were included in our analysis, the mean recruitment rate of trials that did not require written consent was 7.5 participants per month, compared to a

recruitment rate of 8.7 participants per month in trials that required written consent (with the 2 outlier trials excluded) ($p = 0.68$). The predictors of recruitment rate in multivariable analysis with the 2 outliers removed were the number of centers (β 0.25, $p < 0.001$), the number of countries (β -1.55, $p = 0.011$), and the maximum time to intervention (β 0.51, $p = 0.18$).

DISCUSSION This systematic review supports mixed conclusions about the effect of alternatives to written informed consent on recruitment in acute stroke trials. Overall, clinical trials that did not require written consent recruited participants more quickly than clinical trials that required written consent; however, this difference reflects the influence of 2 outliers (PHANTOM-S and HASTA) that differed substantially from other trials in their conduct and the interventions studied. When these 2 outliers are excluded, there is no univariable association between written informed consent and recruitment rate, and such requirements do not predict recruitment rate after adjusting for the number of centers, number of countries, and mRS-based exclusions on multivariable modeling.

On one hand, this analysis supports a negative conclusion: in controlled trials of clinical therapies for acute ischemic stroke delivered in traditional settings (such as an emergency department), alternatives to written informed consent are not associated with more rapid recruitment. As one practical consequence, consider whether a stroke clinical investigator in the United States should seek an Exception from Informed Consent (EFIC) from the Food and Drug Administration for a clinical trial of a new neuroprotective agent. These exceptions allow for the enrollment of participants “who have a life-threatening medical condition that necessitates urgent intervention (for which available treatments are unproven or unsatisfactory), and who, because of their condition (e.g., traumatic brain injury), cannot provide informed consent.”⁵³ However, these exceptions also impose additional burdens that may add to the cost and difficulty of conducting trials, such as the requirement of community consultation in the form of focus groups, town hall meetings, and other forums.^{53,54} Our findings suggest that in trials of clinical therapies delivered in traditional settings after a clinical diagnosis of acute ischemic stroke, such waivers of informed consent are unlikely to facilitate participant recruitment to a degree sufficient to justify the additional burdens of community consultation or the ethical tradeoffs associated with such waivers.

On the other hand, this analysis also supports a limited positive conclusion. Some important trials, like PHANTOM-S and HASTA, do not study the

Figure 3 Recruitment rates of endovascular trials

Markers for individual trials are scaled by the number of participants enrolled. *Second-generation endovascular trials. ESCAPE = Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial; IMS III = Interventional Management of Stroke Trial; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE = Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy; REVASCAT = Randomized Trial of Revascularization with Solitaire FR Device versus Best Medical Therapy in the Treatment of Acute Ischemic Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting within Eight Hours of Symptom Onset; SWIFT = Solitaire with the Intention for Thrombectomy; SWIFT-PRIME = Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke; SYNTHESIS = Local Versus Systemic Thrombolysis for Acute Ischemic Stroke.

effects of different clinical therapies such as devices or drugs, but instead study the effects of systems-level interventions (dispatching mobile stroke units and assigning different priority levels to stroke emergencies) that influence the speed and efficiency with which standard clinical therapies are delivered. Given that acute treatments such as thrombolysis are currently provided to fewer than 5% of patients with acute ischemic strokes,⁵⁵ the greatest future reductions in stroke morbidity may result from research on improving emergency system responses to stroke, rather than from research on new clinical therapies. In many studies at the emergency system level, individual-level consent is not possible because individuals must be randomized prior to emergency response activation. In such cases, waivers of informed consent are critical to the successful conduct of urgently needed studies. In the United States, these studies may be eligible for standard waivers of consent if they involve no more than minimal risk to participants; studies of greater than minimal risk may be eligible for special exception to consent through EFIC.

Cluster-randomized trials. We have categorized Walter et al.⁸ and PHANTOM-S as cluster-randomized clinical trials because individuals were allocated to treatment at a group level (based on the week in which their stroke occurred) rather than at an individual level. In neither case was cluster randomization essential to trial design; individuals could theoretically have been randomized at an individual level to dispatch of a regular ambulance or a mobile stroke unit, but group randomization was chosen for organizational feasibility. In both cases, the unit of randomization was also incidental to the inability to seek written informed consent. That is, even if patients had been randomized at an individual level, randomization would still have taken place prior to ambulance dispatch, and therefore individual consent prior to randomization would not have been possible.

The conduct of cluster-randomized clinical trials is a matter of ongoing ethical and regulatory controversy. While a multinational and multidisciplinary group of scholars recently issued consensus guidelines,⁵⁶ and the US Office of Human Research Protections has issued recommendations on the application of existing regulations to such trials,⁵⁷ appropriate regulation remains a source of confusion and debate.^{58,59}

Limitations. We recognize several limitations of this review. First, there is the potential for publication bias. Because this review relies only upon published journal articles (excluding conference abstracts and other nonpublished material), our inferences are limited to studies that have been completed and

published. Studies with more liberal or unusual protocols for obtaining consent may be systematically excluded from journals that impose ethical standards upon data collection for publication. Studies with more rigid requirements of consent may be more likely to terminate early due to slow enrollment and thus less likely to be published.

A second limitation is that, while the methods of this review enable generalizations about the published literature as a whole, we were unable to examine variation in informed consent within trials. While almost all study authors responded to our specific inquiries, participant-level data on the number of patients who refused or were unable to consent were often unrecorded or collected in a heterogeneous fashion across sites in multicenter studies. This in part reflects inherent difficulties of data collection under the intense time pressure of acute stroke care. In earlier studies of the impact of surrogate consent on recruitment and generalizability,^{12,13} data from individual trials about the number of participants enrolled via surrogate consent as compared with self-consent were useful in establishing the importance of surrogate consent. Closer examination of variation within trials allowing waivers of informed consent may provide valuable insights into the effects of such waivers on recruitment. For future meta-analyses, standard methods are needed for recording the number of patients who refuse consent and who are enrolled via surrogate consent or waivers. However, it is also important that data collection standards do not themselves interfere with trialists' ability to deliver rapid treatment in acute ischemic strokes.

Finally, and most importantly, while our multivariable model accounts for many potential predictors of recruitment rate, it does not account for all predictors. Important predictors that are absent from our analysis include the volume of strokes at each center, the number of competing trials at each center, and the individual commitment of stroke investigators to clinical research. Since we lack disaggregated recruitment data by center (as many trials in this systematic review are multicentered), we are unable to account for possible center-specific variation.

Alternatives to written informed consent in acute stroke trials may enable trial designs that would not be feasible otherwise. Nonetheless, we have not found evidence that, in traditional trial designs, using alternatives to informed consent is associated with higher recruitment rates. These findings are limited by publication bias, the absence of participant-specific data on refusals of consent and on the number who were enrolled via surrogate consent or waivers, and by possible center-specific confounders of recruitment rate (including the capability and commitment of each center to carry out acute stroke trials).

AUTHOR CONTRIBUTIONS

William B. Feldman contributed to the study design, literature review, data analysis, data interpretation, and writing. Anthony S. Kim contributed to the study design, literature review, data interpretation, and writing. S. Andrew Josephson contributed to the study design, data interpretation, and writing. Daniel H. Lowenstein contributed to the study design, data interpretation, and writing. Winston Chiong contributed to the study design, literature review, data analysis, data interpretation, and writing.

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REFERENCES

1. National Institute of Health StrokeNet. Available at: <https://www.nihstroke.net.org/>. Accessed May 19, 2015.
2. Alexandrov AV. Slow recruitment in clinical trials: failure is not an option! *Int J Stroke* 2006;1:160.
3. Goyal M, Almekhlafi M, Menon B, et al. Challenges of acute endovascular stroke trials. *Stroke* 2014;45:3116–3122.
4. Rose DZ, Kasner SE. Informed consent: the rate-limiting step in acute stroke trials. *Front Neurol* 2011;2:65.
5. Kasner SE, Del Giudice A, Rosenberg S, et al. Who will participate in acute stroke trials? *Neurology* 2009;72:1682–1688.
6. Ciccone A, Sterzi R, Crespi V, Defanti CA, Pasetti C. Thrombolysis for acute ischemic stroke: the patient's point of view. *Cerebrovasc Dis* 2001;12:335–340.
7. Demarquay G, Derex L, Nighoghossian N, et al. Ethical issues of informed consent in acute stroke: analysis of the modalities of consent in 56 patients enrolled in urgent therapeutic trials. *Cerebrovasc Dis* 2005;19:65–68.
8. Walter S, Kostopoulos P, Haass A, et al. Diagnosis and treatment of patients with stroke in a mobile stroke unit versus in hospital: a randomised controlled trial. *Lancet Neurol* 2012;11:397–404.
9. Ebinger M, Winter B, Wendt M, et al. Effect of the use of ambulance-based thrombolysis on time to thrombolysis in acute ischemic stroke: a randomized clinical trial. *JAMA* 2014;311:1622–1631.
10. Chiong W, Kim AS, Huang IA, Farahany NA, Josephson SA. Testing the presumption of consent to emergency treatment for acute ischemic stroke. *JAMA* 2014;311:1689–1691.
11. Chiong W, Kim AS, Huang IA, Farahany NA, Josephson SA. Inability to consent does not diminish the desirability of stroke thrombolysis. *Ann Neurol* 2014;76:296–304.
12. Flaherty ML, Karlawish J, Khoury JC, Kleindorfer D, Woo D, Broderick JP. How important is surrogate consent for stroke research? *Neurology* 2008;71:1566–1571.
13. Kane I, Lindley R, Lewis S, Sandercock P. Impact of stroke syndrome and stroke severity on the process of consent in the Third International Stroke Trial. *Cerebrovasc Dis* 2006;21:348–352.
14. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372:11–20.
15. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med* 2015;372:1019–1030.
16. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med* 2015;372:1009–1018.
17. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med* 2015;372:2285–2295.
18. Jovin T, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med* 2015;372:2296–2306.
19. Ginsberg MD, Palesch YY, Martin RH, et al. The albumin in acute stroke (ALIAS) multicenter clinical trial: safety analysis of part 1 and rationale and design of part 2. *Stroke* 2011;42:119–127.
20. Ginsberg MD, Palesch YY, Hill MD, et al. High-dose albumin treatment for acute ischaemic stroke (ALIAS) part 2: a randomised, double-blind, phase 3, placebo-controlled trial. *Lancet Neurol* 2013;12:1049–1058.
21. Zinkstok SM, Roos YB. Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial. *Lancet* 2012;380:731–737.
22. Schäbitz WR, Laage R, Vogt G, et al. AXIS: a trial of intravenous granulocyte colony-stimulating factor in acute ischemic stroke. *Stroke* 2010;41:2545–2551.
23. Ringelstein EB, Thijs V, Norrving B, et al. Granulocyte colony-stimulating factor in patients with acute ischemic stroke: results of the AX200 for Ischemic Stroke trial. *Stroke* 2013;44:2681–2687.
24. Bi M, Ma Q, Zhang S, et al. Local mild hypothermia with thrombolysis for acute ischemic stroke within a 6-h window. *Clin Neurol Neurosurg* 2011;113:768–773.
25. Heiss WD, Brainin M, Bornstein NM, Tuomilehto J, Hong Z. Cerebrolysin in patients with acute ischemic stroke in Asia: results of a double-blind, placebo-controlled randomized trial. *Stroke* 2012;43:630–636.
26. Lang W, Stadler CH, Poljakovic Z, Fleet D. A prospective, randomized, placebo-controlled, double-blind trial about safety and efficacy of combined treatment with alteplase (rt-PA) and cerebrolysin in acute ischaemic hemispheric stroke. *Int J Stroke* 2013;8:95–104.
27. Pancioli AM, Adeoye O, Schmit PA, et al. Combined approach to lysis utilizing eptifibatide and recombinant tissue plasminogen activator in acute ischemic stroke-enhanced regimen stroke trial. *Stroke* 2013;44:2381–2387.
28. Berglund A, Svensson L, Sjostrand C, et al. Higher pre-hospital priority level of stroke improves thrombolysis frequency and time to stroke unit: the Hyper Acute STroke Alarm (HASTA) study. *Stroke* 2012;43:2666–2670.
29. Hemmen TM, Raman R, Guluma KZ, et al. Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L): final results. *Stroke* 2010;41:2265–2270.
30. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med* 2013;368:893–903.
31. Rosso C, Corvol JC, Pires C, et al. Intensive versus subcutaneous insulin in patients with hyperacute stroke:

- results from the randomized INSULINFARCT trial. *Stroke* 2012;43:2343–2349.
32. 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.
33. Kimura K, Aoki J, Sakamoto Y, et al. Administration of edaravone, a free radical scavenger, during t-PA infusion can enhance early recanalization in acute stroke patients—a preliminary study. *J Neurol Sci* 2012;313:132–136.
34. Lees KR, Bornstein N, Diener HC, Gorelick PB, Rosenberg G, Shuaib A. Results of membrane-activated chelator stroke intervention randomized trial of DP-b99 in acute ischemic stroke. *Stroke* 2013;44:580–584.
35. Kidwell CS, Jahan R, Gornbein J, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med* 2013;368:914–923.
36. Padma MV, Bhasin A, Bhatia R, et al. Normobaric oxygen therapy in acute ischemic stroke: a pilot study in Indian patients. *Ann Indian Acad Neurol* 2010;13:284–288.
37. Shaw L, Price C, McLure S, et al. Paramedic initiated lisinopril for acute stroke treatment (PIL-FAST): results from the pilot randomised controlled trial. *Emerg Med J* 2014;31:994–999.
38. Piironen K, Tiainen M, Mustanoja S, et al. Mild hypothermia after intravenous thrombolysis in patients with acute stroke: a randomized controlled trial. *Stroke* 2014;45:486–491.
39. Hougaard KD, Hjort N, Zeidler D, et al. Remote ischemic preconditioning as an adjunct therapy to thrombolysis in patients with acute ischemic stroke: a randomized trial. *Stroke* 2014;45:159–167.
40. Ankolekar S, Fuller M, Cross I, et al. Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke: the rapid intervention with glyceryl trinitrate in Hypertensive Stroke Trial (RIGHT, ISRCTN66434824). *Stroke* 2013;44:3120–3128.
41. Torgano G, Zecca B, Monzani V, et al. Effect of intravenous tirofiban and aspirin in reducing short-term and long-term neurologic deficit in patients with ischemic stroke: a double-blind randomized trial. *Cerebrovasc Dis* 2010;29:275–281.
42. Skoloudik D, Fadna T, Roubec M, et al. Changes in hemocoagulation in acute stroke patients after one-hour sono-thrombolysis using a diagnostic probe. *Ultrasound Med Biol* 2010;36:1052–1059.
43. Staszewski J, Brodacki B, Kotowicz J, Stepień A. Intravenous insulin therapy in the maintenance of strict glycemic control in nondiabetic acute stroke patients with mild hyperglycemia. *J Stroke Cerebrovasc Dis* 2011;20:150–154.
44. Demaerschalk BM, Bobrow BJ, Raman R, et al. Stroke team remote evaluation using a digital observation camera in Arizona: the initial mayo clinic experience trial. *Stroke* 2010;41:1251–1258.
45. Saver JL, Jahan R, Levy EI, et al. Solitaire flow restoration device versus the merci retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet* 2012;380:1241–1249.
46. Ciccone A, Valvassori L, Nichelatti M, et al. Endovascular treatment for acute ischemic stroke. *N Engl J Med* 2013;368:904–913.
47. Ciccone A, Valvassori L, Ponzio M, et al. Intra-arterial or intravenous thrombolysis for acute ischemic stroke? The SYNTHESIS pilot trial. *J Neurointerv Surg* 2010;2:74–79.
48. Haley EC Jr, Thompson JL, Grotta JC, et al. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. *Stroke* 2010;41:707–711.
49. Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med* 2012;366:1099–1107.
50. Nogueira RG, Lutsep HL, Gupta R, et al. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet* 2012;380:1231–1240.
51. Chamorro A, Amaro S, Castellanos M, et al. Safety and efficacy of uric acid in patients with acute stroke (URICO-ICTUS): a randomised, double-blind phase 2b/3 trial. *Lancet Neurol* 2014;13:453–460.
52. Yan L, Li YD, Li YH, Li MH, Zhao JG, Chen SW. Outcomes of antiplatelet therapy for haemorrhage patients after thrombolysis: a prospective study based on susceptibility-weighted imaging. *Radiol Med* 2014;119:175–182.
53. Guidance for Institutional Review Boards. Clinical investigators, and sponsors: exception from informed consent requirements for emergency research. Available at: <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM249673.pdf>. Accessed May 19, 2015.
54. Protection of human subjects: informed consent: FDA: final rule. *Fed Regist* 1996;61:51498–51533.
55. Kleindorfer D, De Los Rios La Rosa F, Khatri P, Kissela B, Mackey J, Adeoye O. Temporal trends in acute stroke management. *Stroke* 2013;44(suppl 1):2013–2016.
56. Taljaard M, Weijer C, Grimshaw JM. The Ottawa Statement on the ethical design and conduct of cluster randomised trials: précis for researchers and research ethics committees. *BMJ* 2013;346:f2838.
57. Recommendations on Regulatory Issues in Cluster Studies. Available at: <http://www.hhs.gov/ohrp/sachrp/mtgngs/mtg03-14/clusterstudiesrecommendations.html>. Accessed May 19, 2015.
58. Macklin R. Cluster randomized trials: another look. *Hastings Cent Rep* 2014;44:37–43.
59. van der Graaf R, Koffijberg H, Grobbee DE, et al. The ethics of cluster-randomized trials requires further evaluation: a refinement of the Ottawa Statement. *J Clin Epidemiol* 2015;68:1108–1114.
60. Sandercock P, Lindley R, Wardlaw J, et al. Third International Stroke Trial (IST-3) of thrombolysis for acute ischaemic stroke. *Trials* 2008;9:1–17.