



University
of Glasgow

Dani, K.A., McCormick, M.T. and Muir, K.W. (2008) *Brain lesion volume and capacity for consent in stroke trials: potential regulatory barriers to the use of surrogate markers*. Stroke, 39 (8). pp. 2336-2340.
ISSN 0039-2499

<http://eprints.gla.ac.uk/17845/>

Deposited on: 19 January 2012

Stroke

American Stroke
AssociationSM

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Division of American
Heart Association



Brain Lesion Volume and Capacity for Consent in Stroke Trials : Potential Regulatory Barriers to the Use of Surrogate Markers

Krishna A. Dani, Michael T. McCormick and Keith W. Muir

Stroke 2008, 39:2336-2340: originally published online June 5, 2008

doi: 10.1161/STROKEAHA.107.507111

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214
Copyright © 2008 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online
ISSN: 1524-4628

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://stroke.ahajournals.org/content/39/8/2336>

Subscriptions: Information about subscribing to *Stroke* is online at
<http://stroke.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters
Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax:
410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Brain Lesion Volume and Capacity for Consent in Stroke Trials

Potential Regulatory Barriers to the Use of Surrogate Markers

Krishna A. Dani, MRCP; Michael T. McCormick, MRCP; Keith W. Muir, MD, FRCP

Background and Purpose—European directives and legislation in some countries forbid inclusion of subjects incapable of consent in research if recruitment of patients capable of consent will yield similar results. We compared brain lesion volumes in stroke patients deemed to have capacity to consent with those defined as incapacitated.

Methods—Data were obtained from 3 trials recruiting patients primarily with cortical stroke syndromes. Patients were recruited within 24 hours of onset and used MRI based selection or outcome criteria. Method of recruitment was recorded with stroke severity, age, and brain lesion volumes on Diffusion Weighted Imaging.

Results—Of the 56 subjects included, 38 (68%) were recruited by assent and 18 (32%) by consent. The assent group had a median lesion volume of 18.35 cubic centimetres (cc) (interquartile range [IQR] 8.27–110.31 cc), compared to 2.79 cc (IQR 1.31–12.33 cc) when patients consented ($P=0.0004$). Lesions were smaller than 5 cc in 7/38 (18%) in the assent group and 11/18 (61%) in the consent group ($P=0.0024$). There was good correlation between neurological deficit by NIH stroke scale score and lesion volume ($r=0.584$, $P<0.0001$). Logistic regression demonstrated NIHSS or lesion volume predicted capacity to consent.

Conclusions—Patients with acute stroke who retain capacity to consent have significantly smaller infarct volumes than those incapable of consent, and these are frequently below the limits where measurement error significantly compromises valid use of volumetric end points. Only a small proportion of patients with capacity to consent would be eligible for, and contribute usefully to, most acute stroke trial protocols. (*Stroke*. 2008;39:2336-2340.)

Key Words: clinical trials ■ informed consent ■ magnetic resonance imaging ■ ethics

The Declaration of Helsinki¹ stipulates that patients who are incapable of consent “. . . should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.” This allows for research participation by incapacitated individuals provided that the interests of the patient group overall are best served by such participation. However, the more recent European Clinical Trials Directive (ECTD)² stipulates that if the “same results” could be achieved by recruitment of persons who are capable of consent, then subjects should not be recruited by assent. The position is further complicated by locale-specific legal protections, such as the Adults With Incapacity Act in Scotland,³ which states that the research must provide “real and direct benefit to the adult or to other persons having the same incapacity.”

One fundamental issue regarding participation by acute stroke patients in clinical trials is whether there are important differences between those with and without capacity to consent. If there is no difference, then both the Declaration of Helsinki and the ECTD advise that only those with capacity to consent should

be included. Demarquay and colleagues⁴ showed that capacity diminishes with increasing age and baseline neurological deficit. Similarly, data from the first 300 patients recruited to the third International Stroke Trial (IST3)⁵ show that those with more severe stroke were less likely to have been recruited by consent, with clinical syndrome being an important determinant.

Brain imaging is increasingly included as a biomarker of treatment effect in clinical trials, and trials designed with imaging end points generally include imaging selection criteria. We hypothesized that imaging based trials, and indeed most acute stroke trials, would be significantly compromised if recruitment were restricted to subjects who retain capacity. We therefore assessed the lesion volumes from patients included in 3 studies of acute stroke at our institution and compared the volumes in those who had been recruited by consent to those recruited by assent.

Methods

Studies

Three acute stroke studies that used magnetic resonance imaging (MRI) in our institution were identified. All studies had been approved by local

Received October 29, 2007; final revision received December 13, 2007; accepted January 3, 2008.

From the Division of Clinical Neurosciences, University of Glasgow, Institute of Neurological Sciences, Southern General Hospital, Glasgow, Scotland, UK. Correspondence to Dr Keith Muir, Division of Clinical Neurosciences, University of Glasgow, Institute of Neurological Sciences, Southern General Hospital, Glasgow G51 4TF, Scotland, UK. E-mail k.muir@clinmed.gla.ac.uk

© 2008 American Heart Association, Inc.

Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.107.507111

Table. Baseline Data in Each Group

	Assent Group	Consent Group	Differences Between Groups (<i>P</i> Value)
Total No. of patients (% of total)	38 (68%)	18 (32%)	...
Mean age, ±SD	71±11.2	68±12.7	0.398 (Mann–Whitney)
Mean time to imaging, ±SD	17.1±7.1	14.3±7.3	0.143 (Mann–Whitney)
No. of patients receiving rtPA (% of group)	10 (26%)	2 (11%)	0.2168 (Fisher Exact)
Mean time to rtPA, mins±SD	166±23	177±3.5	0.564 (Mann–Whitney)
Clinical syndrome, No. of patients (%)			
TACS	20 (53%)	3 (17%)	0.0231*
PACS	11 (29%)	9 (50%)	(Fisher-Freeman-Halton Exact)
LACS	5 (13%)	6 (33%)	
POCS	2 (5%)	0 (0%)	
Site of occlusion			
ICA	3	0	0.594
M1, MCA	5	1	(Fisher-Freeman-Halton Exact)
M2, MCA	1	1	
PCA	1	1	
Unidentified	13	6	
Left:right hemisphere stroke	11:7	20:17	0.638 (Chi ²)
Lesions <5 cc (%)	11/18 (61%)	7/38 (18.4%)	0.0024 (Chi ²)
Median lesion volume (cc) [IQR]	18.35 (8.27–110.3)	2.79 (1.31–12.33)	0.0004 (Mann–Whitney)

The differences in clinical syndrome between the groups are statistically significant (*P*=0.0231, Fisher-Freeman-Halton Exact Test). The site of occlusion is also documented for all cases where angiography was performed.

TACS indicates total anterior circulation stroke; PACS, partial anterior circulation stroke; LACS, lacunar stroke; POCS, posterior circulation stroke; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; cc, cubic centimeters. Note 1 patient in the Assent group had bilateral lesions.

*Statistically significant, *P*<0.05.

or national Research Ethics Committees. Studies 1 and 2 were conducted after the ECTD and local legislation on Adults with Incapacity, while study 3 predated these. Studies 1 and 2 were single-site, imaging-based studies, whereas study 3 was a multi-center neuroprotectant trial. All 3 studies recruited patients primarily with cortical stroke syndromes, whereas Study 3 also included subjects with lacunar syndromes. Studies 1 and 2 performed scans within 24 hours and study 3 scanned patients within 12 hours of ictus. Scans were performed using either a 1.5T or a 3T MRI scanner. All 3 studies permitted recruitment either by consent or by assent from relatives. The capacity of individual subjects was assessed only by the randomizing clinician. Consent or assent was obtained in all cases by an experienced stroke neurologist, physician, or research fellow, with the most senior investigator involved being recorded. Patients from these studies were included if digital copies of the initial MRI scans were available for review. Medical files for these patients were retrieved, and data describing the recruitment method, baseline demographic data, and neurological deficit were recorded.

Clinical Data

The following data were recorded for each individual: age, sex, stroke lateralization, clinical syndrome using the Oxfordshire Community Stroke Project (OCSP),⁶ stroke severity by the National Institutes of Health Stroke Scale (NIHSS),⁷ time to imaging, and whether or not an individual was treated with recombinant tissue Plasminogen Activator (rt-PA).

Image Analysis

Lesion volumes on admission were retrospectively assessed by 2 individuals; M.T.M. (Studies 2 and 3) and K.A.D. (study 1). The software package Cheshire (Perceptive Informatics, PAREXEL) was used to calculate lesion volumes on diffusion weighted imaging (DWI) sequences. After identification of the lesion by the rater, a semiautomated method was used to define lesion borders on each

slice. Further manual refinement on each slice produced final lesion boundaries. The lesion volume was then calculated automatically. Where available, formal reports of angiographic examinations (CT angiography and time of flight magnetic resonance angiography) by experienced neuroradiologists were reviewed and the site of any occlusion noted. Results of perfusion imaging, when undertaken, were also assessed.

Statistical Analysis

Statistical analyses were mainly performed with Minitab (Version 14.0). The distribution of data were assessed using a Kolmogorov–Smirnov Test, and a Mann–Whitney test was subsequently used to investigate whether lesion volumes in the group recruited by assent differed from those of the group recruited by consent. Spearman’s Rank test was used to assess the correlation between admission NIHSS score and lesion volume. A number of other clinical parameters were compared between groups (Table). Finally a binary logistic regression analysis was performed to determine the effects of NIHSS, lesion volume, age, and lateralization on the capacity to consent (SPSS v14.0).

Results

Baseline Data

Scans from 56 patients were analyzed. Thirty-eight patients (68%) were recruited by assent and 18 patients (32%) by consent. Studies 1, 2, and 3 contributed 15, 29, and 12 patients, respectively, with 33%, 21%, and 58% of patients being recruited by consent in these studies. Baseline characteristics for the assenting and consenting groups are given in the Table.

Four investigators were involved: K.M. recruited 13, M.T.M. recruited 25, K.A.D. recruited 14. One other inves-

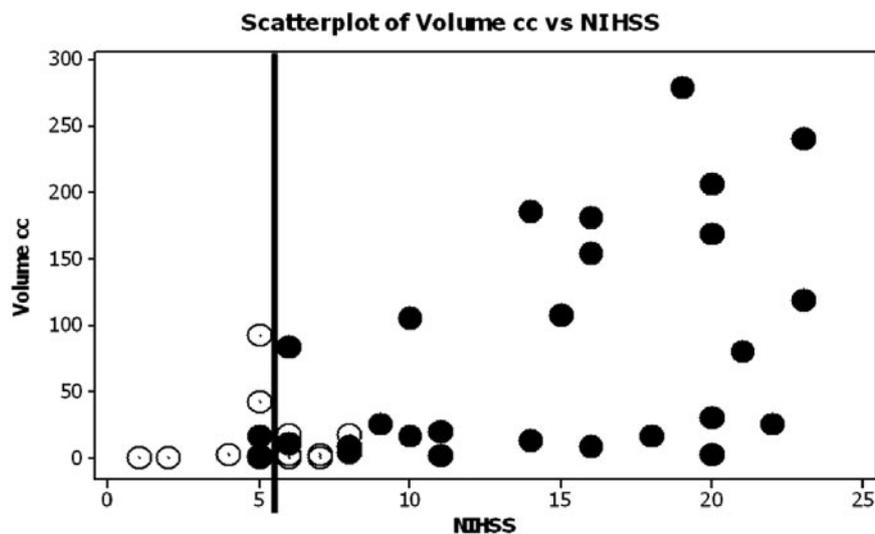


Figure. Scatterplot showing the relationship of NIHSS to lesion volume. Open circles represent the "consent" group, and black circles represent the "assent" group. The vertical black line represents the lower NIHSS threshold for the inclusion criteria in some stroke studies, eg, DEFUSE.

tigator recruited only 1 patient, and data regarding recruiting investigator were not available for 3 patients. Among the 3 main recruiting investigators there were no differences in lesion volume ($P=0.15$ Kruskal-Wallis), the proportions recruited by assent (46% $\frac{13}{28}$, 80% $\frac{29}{36}$, and 71% $\frac{19}{27}$; $P=0.118$, Fisher-Freeman-Halton Exact test), the proportion with left hemisphere strokes ($P=0.506$, Fisher Freeman Halton), or of median NIHSS score ($P=0.800$, Kruskal-Wallis). There was no significant difference in lesion volume ($P=0.6511$, Mann-Whitney) or median NIHSS ($P=0.1528$, Mann-Whitney) between those with right hemisphere strokes compared with those with left hemisphere strokes. Perfusion imaging (PWI) was available for 7 patients, of whom none had PWI-DWI mismatch, consistent with the late imaging time in most cases.

The distribution of clinical syndromes defined by OCSF criteria differed significantly between groups (Table; $P=0.0231$, Fisher-Freeman-Halton Exact test). There was a trend toward more proximal occlusion in the assenting group but this did not reach statistical significance ($P=0.594$, Fisher-Freeman-Halton Exact).

Lesion Volume in Assent and Consent Groups

Lesion volume data were not of normal distribution ($P<0.010$, Kolmogorov-Smirnov) and were positively skewed. The assenting group had a median lesion volume of 18.35 cubic centimetres (cc) (interquartile range [IQR] 8.27 to 110.31 cc) and a mean (\pm SD) of 63.7 cc (\pm 78.5). In the consenting group, the median lesion volume was 2.79 cc (IQR 1.31 to 12.33 cc) with a mean (\pm SD) of 12.1 cc (\pm 23.1). Lesion volumes of assenting patients were significantly greater than those of consenting patients (upper tailed Mann-Whitney test, $P=0.0004$). Statistical significance remained when the 14 patients treated with rt-PA were excluded to ensure that there was no confounding effect of reperfusion ($P=0.002$; $n=42$): mean, median, and IQR volumes were 66 cc, 16.9 cc, and 8.6 to 118 cc for the assenting group and 7.9 cc, 3.6 cc, and 1.8 to 9.9 cc for the consenting group.

Predictive Factors for Capacity to Consent

There was a positive correlation between NIHSS and lesion volume (Figure; $n=42$, Spearman Rank Correlation coefficient

$r=0.584$; $P<0.0001$). When patients who received rt-PA were excluded from this analysis, the correlation was similar ($n=32$, $r=0.587$, $P=0.001$). Follow-up NIHSS data were available for 34 patients; 2 patients at day 3 and 32 patients at day 7. There was no difference in lesion volumes between those patients who demonstrated an improvement in NIHSS $>40\%$ (14 patients) compared to those who did not ($P=0.20$, Mann-Whitney, $n=20$).

In a binary logistic regression model to predict capacity to consent, including lesion volume, stroke lateralization, age, and NIHSS, the only significant univariate predictor was NIHSS ($n=38$, $P=0.017$). Lesion volume was of borderline significance ($n=55$, $P=0.052$). When both NIHSS and lesion volume were included in the model, only NIHSS was significant ($n=38$, odds ratio 0.13 [95% confidence interval 0.23 to 0.742] per 4 point increase in NIHSS score, $P=0.022$).

Discussion

Our findings support the need to recruit patients to trials by assent. We found significant differences in lesion volume, stroke severity, and clinical syndrome between those recruited by consent compared to those recruited by assent. Unsurprisingly we demonstrated that NIHSS is the best predictor of capacity to consent.

Two central ethical questions prompted by considering the application of the European Clinical Trials Directive in acute stroke trials are (1) whether there are reasons to expect differences in the biology of stroke in those able to consent from those recruited by assent that would compromise the end points for a trial; and (2) whether there are other practical issues that prevent clinically useful data being obtained from consenting patients. Imaging has the potential to identify the most appropriate subset of patients for recruitment, meaning fewer subjects may be required to produce informative data.⁸ However, it will be additionally important to know whether capacity for consent might signify a different biological response. Current indirect data suggest it does. For example, admission lesion volume is an independent predictor of intracerebral hemorrhage after the administration of intrave-

nous thrombolytic therapy,⁹ suggesting an increased risk in patients in the assenting group. In those patients deemed capable of consent, we found a predominance of lacunar syndromes, and distal MCA occlusions associated with lesser neurological deficit. Therefore this cohort is unlikely to provide useful data regarding reperfusion or recanalization. Many of these patients are likely to improve spontaneously, unlike the larger strokes seen in the assent group. Therefore it is clear that significant differences exist in stroke etiology, presentation, natural history, and prognosis between consenting and assenting groups, and conclusions made from one cohort may not be applicable to the other.

With regard to the second issue, to find evidence of a biological effect, either by change in neurological impairment or by lesion volume, the test instruments used must be sensitive to the degree of change expected. Exclusion of patients with brain lesion volumes under 5 cc has been proposed because measurement error is too great to produce reliable results.¹⁰ If a change in radiological parameters is not measurable reliably, recruitment of a subject might be regarded as ethically dubious, irrespective of an individual's capacity. Of note, only 13% of patients recruited by assent had lesion volumes less than 5 cc, suggesting that even measurement error in imaging-based trials may be less in the assenting group.

What would have been the effect in our center of restricting recruitment to patients capable of consent? Typical inclusion criteria for imaging-based trials include both clinical measures of stroke severity selection and lesion size.^{10–14} If criteria such as minimum NIHSS score of 6 (as used in DEFUSE¹¹) and minimum lesion volume of 5 cc (to reduce measurement error¹⁰) were applied to our population, recruitment by consent alone would have resulted in only 4 patients (7%) being included, all of whom still had relatively small lesions (<20 cc). Of the remaining 28 patients where NIHSS data were available, 25 of these could also be included if assent was allowed. Therefore, if assent were not possible recruitment of the remaining eligible patients would allow only limited conclusions to be made, thus potentially leading to a situation of unethical recruitment of these “eligible” patients. Many stroke trials which are not primarily imaging-based also specify a minimum neurological deficit (NIHSS) for inclusion, and thus these issues are applicable to stroke trials in general.

The validity of consent is questionable in neurological disease and in acute illness. Even acute stroke patients eligible for thrombolysis who recover rapidly have limited recall of the nature of their event,¹⁵ and in subarachnoid hemorrhage trials only 28% of patients felt that they had been capable of making an adequate decision.¹⁶ In this regard it is vital that the information sheets provided to patients in acute trials are clear and concise and aimed at patients with little medical knowledge.

Our findings relate to practice at a single site but behavior with respect to consent appeared reasonably consistent across a number of different investigators and studies, although clearly all were practicing in the same environment. Our site is experienced in recruitment to clinical trials in acute stroke

and has not noted any substantial differences in interpretation of recruitment processes compared to other sites in any multicenter trial. The population described here is fairly typical of those in stroke trials.

We did not assess lesion localization or morphology. Our cohort is not entirely homogeneous with minor differences in time window of recruitment and clinical syndromes permitted between studies. We cannot exclude the possibility that knowledge of lesion volume might have influenced the decision regarding appropriate means of recruitment, but MRI was seldom used as the primary imaging modality during the period of these studies. We did not have repeated data on vessel occlusion or perfusion status, but findings remained significant after excluding rt-PA-treated patients whose initial NIHSS score may not have reflected accurately the DWI lesion volume attributable to reperfusion before imaging.

In conclusion, this study demonstrates that lesion volumes are greater in patients recruited to acute stroke studies by assent compared to consent. Given the biological and clinical differences between small and large lesions, and the methodological restrictions imposed by small lesions, this emphasizes the importance of recruitment by assent to many acute stroke studies. Neither safety nor efficacy outcomes may be measurably reliable from consenting patients alone, with effects on sample size, study duration, and validity of conclusions that may have a wider and potentially negative impact.

Disclosures

The authors are currently recruiting patients to a single-site imaging-based study by both assent and consent and have sought ethical approval for several imaging-based clinical trials, some of which have been refused for reasons pertaining to capacity to consent.

References

1. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *J Postgrad Med.* 2002;48:206–208.
2. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. *Med Etika Bioet.* 2002;9:12–19.
3. Scotland. Adults with incapacity (Scotland) Act 2000—excerpt. *Bull Med Ethics.* 2000;157:8–11.
4. Demarquay G, Derex L, Nighoghossian N, Adeleine P, Philippeau F, Honnorat J, Trouillas P. 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.
5. Kane I, Lindley R, Lewis S, Sandercock P. IST-3 Collaborative Group. Impact of stroke syndrome and stroke severity on the process of consent in the Third International Stroke Trial. *Cerebrovasc Dis.* 2006;21:348–352.
6. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet.* 1991;337:1521–1526.
7. Brott T, Adams HP Jr, Olinger CP, Marler JR, Barsan WG, Biller J, Spilker J, Holleran R, Eberle R, Hertzberg V. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke.* 1989;20:864–870.

8. Muir KW. Heterogeneity of stroke pathophysiology and neuroprotective clinical trial design. *Stroke*. 2002;33:1545–1550.
9. Selim M, Fink JN, Kumar S, Caplan LR, Horkan C, Chen Y, Linfante I, Schlaug G. Predictors of hemorrhagic transformation after intravenous recombinant tissue plasminogen activator: prognostic value of the initial apparent diffusion coefficient and diffusion-weighted lesion volume. *Stroke*. 2002;33:2047–2052.
10. Warach S. New imaging strategies for patient selection for thrombolytic and neuroprotective therapies. *Neurology*. 2001;57:S48–S52.
11. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, Bammer R, Kakuda W, Lansberg MG, Shuaib A, Coplin W, Hamilton S, Moseley M, Marks MP. DEFUSE Investigators. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Ann Neurol*. 2006;60:508–517.
12. Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, Sachara C, Soehngen M, Warach S, Hacke W. DEDAS Investigators. Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS): evidence of safety and efficacy 3 to 9 hours after stroke onset. *Stroke*. 2006;37:1227–1231.
13. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, Fischer M, Furlan A, Kaste M, Lees KR, Soehngen M, Warach S. DIAS Study Group. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke*. 2005;36:66–73.
14. Butcher KS, Parsons M, MacGregor L, Barber PA, Chalk J, Bladin C, Levi C, Kimber T, Schultz D, Fink J, Tress B, Donnan G, Davis S. EPITHET Investigators. Refining the perfusion-diffusion mismatch hypothesis. *Stroke*. 2005;36:1153–1159.
15. Grotta J, Bratina P. Subjective experiences of 24 patients dramatically recovering from stroke. *Stroke*. 1995;26:1285–1288.
16. Schats R, Brilstra EH, Rinkel GJ, Algra A, Van Gijn J. Informed consent in trials for neurological emergencies: the example of subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry*. 2003;74:988–991.