Accepted Manuscript

Clinical study

Recruitment to trials of late thrombolysis: Lessons from the EXTEND study

Marie Dagonnier, David W. Howells, Geoffrey A. Donnan, Helen M. Dewey

PII: S0967-5868(14)00033-2

DOI: <http://dx.doi.org/10.1016/j.jocn.2013.10.033>

Reference: YJOCN 5482

To appear in: *Journal of Clinical Neuroscience*

Received Date: 23 January 2013

Accepted Date: 25 October 2013

Please cite this article as: M. Dagonnier, D.W. Howells, G.A. Donnan, H.M. Dewey, Recruitment to trials of late thrombolysis: Lessons from the EXTEND study, *Journal of Clinical Neuroscience* (2014), doi: <http://dx.doi.org/10.1016/j.jocn.2013.10.033>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

D-13-00177

Clinical Studies

Recruitment to trials of late thrombolysis: Lessons from the EXTEND study

Marie Dagonnier^{a,b,*} David W. Howells^a, Geoffrey A. Donnan^{a,b,c}, Helen M. Dewey^{a,b,c}

^a National Stroke Research Institute, The Florey Institute for Neurosciences and Mental Health, Melbourne Brain Centre, Austin Campus, 245 Burgundy Street, Heidelberg, VIC 3084, Australia

^b University of Melbourne, Melbourne, VIC, Australia

^c Department of Neurology, Austin Health, Heidelberg, VIC, Australia

*Corresponding author. Tel.: +61 3 9035 7204.

E-mail address: marie.dagonnier@unimelb.edu.au (M. Dagonnier).

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

Abstract

To increase the percentage of acute stroke patients benefiting from thrombolysis, the utility of expanding the time window of treatment beyond 4.5 hours after stroke onset needs to be investigated. We aimed to identify the target population and challenges of recruitment of patients for the time window beyond 4.5 hours. Extending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND), a multicentre randomised controlled trial testing the efficacy of thrombolytic therapy in patients with clinically significant ischaemic penumbra between 4.5 to 9 hours after stroke onset, was used as a model to evaluate inclusion and exclusion criteria for late thrombolysis trials. Data from all stroke patients admitted to Austin Health over a 1 year period were retrospectively analysed. Case notes were examined to determine potential trial eligibility. Of 556 patients assessed, 95 (17%) presented during the EXTEND time window. Sixty-seven of these (70.5%) were wake-up strokes (WUS) and 28 (29.5%) arrived between 4.5 and 9 hours after symptoms onset. At least one exclusion criterion was found for 78 (82%) of them. Hence, 17 (3%) patients arrived within an appropriate time frame for the study without any exclusion criteria. Most of these (13) arrived outside routine MRI hours. The number of patients recruited would have increased more than three-fold if imaging had been available 24 hours, 7 days a week. A significant proportion (17%) of ischaemic stroke patients presented between 4.5 and 9 hours after stroke onset. The majority of these were WUS. The major challenge identified for patient recruitment was imaging availability.

Keywords: Clinical trials; Imaging; Recruitment; Stroke; Thrombolysis

1. Introduction

Stroke is the third most common cause of death in most Western countries and the major cause of disability (1-3). The incidence of acute stroke events is greater than that of acute coronary events although the resources and acute interventions available do not match this state of affairs (4).

The most specific and biologically powerful treatment for acute ischaemic stroke is thrombolysis with recombinant tissue plasminogen activator (tPA) given within the first 4.5 hours after ischaemic stroke onset (5) but this therapy is disappointingly underused (6). Indeed, only 2–6% of eligible patients receive therapy in most centres (7-13) and approximately 10% in the best performing centres (14,15). One major reason for this is the brevity of the therapeutic time window at 4.5 hours (5,7,16,17) so that the number of patients arriving at emergency centres in time is low.

An important approach to increase the percentage of acute stroke patients who may benefit from thrombolysis has been to investigate the utility of expanding the time window for the use of tPA (16,18-22). An example of this is the ongoing Extending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial which began in March 2010. The primary objective of this randomised, multicentre, double blinded, placebo controlled phase 3 study is to test the hypothesis that selected ischaemic stroke patients with significant penumbral mismatch will have improved clinical outcomes when given tPA up to 9 hours after onset of stroke in comparison to those treated with standard stroke unit care without intravenous tPA (23).

In the trial, stroke patients arriving between 4.5 and 9 hours after symptom onset and meeting both the general and MRI inclusion criteria (Table 1) are randomised to intravenous tPA or placebo groups.

The sample size required is approximately 400 participants, 200 of whom would come from the Asia Pacific region and the remainder in a parallel European study. With up to 20 sites recruiting in Australia and New Zealand and further sites soon to commence in Taiwan and Singapore, it was important to understand the recruitment potential and barriers to facilitate rapid recruitment. Also, should this time window become part of routine management of stroke patients, this information would be useful to health care providers generally.

Hence, using EXTEND as an example, we aimed to identify the target population, the potential barriers to recruitment and ways that these may be overcome to maximise recruitment for time windows beyond 4.5 hours.

2. Methods

Data from all stroke patients admitted to Austin Health over a 1 year period (1 March 2010 to 28 February 2011) were retrospectively analysed. Austin Health is one of the major stroke centres in the Melbourne metropolitan area and one of the first centres activated for EXTEND.

Strokes were categorised according to the time window between symptom onset and arrival in the Emergency Department (ED) in three different groups: patients arriving within 4.5 hours, between 4.5 and 9 hours and those beyond 9 hours.

Identification of wake-up strokes (WUS) was done by reviewing the case notes for all stroke patients arriving to the ED commencing at 12 midnight and going forward by periods of 1 hour until 13:00, at which time all patients were outside the time window for the study.

As for other strokes, WUS were classified into time window categories. WUS onset times were calculated as defined by the study (Table 1).

The case notes of all patients arriving between 4.5 and 9 hours after stroke onset were examined and exclusion criteria for EXTEND (Table 2) were assessed. When more than one exclusion criterion was identified, the less modifiable factor has been considered as the cause of the non-inclusion (for example, in a patient presenting with intracerebral haemorrhage [ICH] and pre-stroke modified Rankin Scale score ≥ 2 , ICH has been considered the main criterion for exclusion).

Time of arrival was also recorded and classified in two groups: outside or inside office hours. Office hours were defined as hours where MRI was available for the trial. At Austin Health, MRI was available for EXTEND patients from 8:30 am to 4:30 pm during week days. No patient could have been included either in the cohort or the trial arm of the study outside of these hours.

3. Results

Between 1 March 2010 and 28 February 2011 a total of 556 patients presented with a final diagnosis of stroke at Austin Health.

Ninety-five patients (17% of total strokes) arrived within the EXTEND time window. Sixty-seven (70.5%) of these strokes were WUS and 28 patients arrived between 4.5 and 9 hours after symptom onset (Fig. 1).

Regarding ischaemic strokes ($n = 368$), 21% ($n = 81$) arrived in the EXTEND time frame and were therefore potentially eligible for late thrombolysis.

Regardless of the exclusion criteria, 60% of the patients presenting within the EXTEND time window arrived in the ED outside office hours (Fig. 2).

At least one exclusion criterion was found for 78 (82%) patients arriving within the trial time window (Fig. 3). Twenty patients were excluded from the study because of the presence of early ischaemic signs on CT scan performed on admission. The second most frequent exclusion criterion was the presence of an ICH in 14 patients. Rapidly improving symptoms and too mild clinical severity, defined by the study as a National Institutes of Health Stroke Scale score less than 4, were also identified as the major reason for exclusion in 12 and 14 patients, respectively. All identified exclusion criteria and the number of patients affected by each of them are shown in Figure 4.

Recent cardiac arrest with cardiac and pulmonary resuscitation were identified as exclusion criteria in one patient and classified as “hazardous condition for tPA”. Renal failure and its related contra-indication to contrast agent was also identified in one patient.

During the 12 month review period, 18% of the patients ($n = 17$) presenting in the accepted window were finally eligible for the trial. Thirteen of these (76%) arrived outside office hours (defined as between 8:30 am and 4:30 pm, Monday to Friday). Therefore combining exclusion criteria, time window after stroke onset and imaging availability, only four patients could have been investigated for randomisation if Austin Health was an active centre during all the analysed time period (Fig. 5).

4. Discussion

The main aim of our study was to identify challenges to recruitment of patients beyond the 4.5 hour limit for thrombolysis which currently exists. Interestingly, 17% of patients presented within the 4.5–9 hour time window and represent an important group of patients who currently receive no therapeutic intervention. We found that the main issue facing the potential management of this group using thrombolysis was 24 hour access to imaging. By identifying this matter early, we have been able to modify our approach by introducing a more flexible and complimentary imaging tool, computed tomography perfusion (CTP) scanning, to overcome recruiting challenges. Indeed, our study highlights the fact that recruitment to stroke trials is often very challenging and may require protocol amendments to solve unexpected problems (24-27). Even though this issue is internationally recognised, it is rarely reported. Insufficient or slow recruitment may have dramatic consequences on the trial length and costs, the validity of the results or the continuation of the study. Unwillingness to participate, complex protocols and eligibility criteria, and trial fatigue by investigators have been identified as the main reasons for difficulty in recruiting people after stroke (26). Known as the “funnel effect” phenomenon, researchers also have the tendency to overestimate the number of available patients who meet the inclusion criteria and would be willing to enrol in a particular trial (28). Investigator driven trials with funding from national funding agencies have more limited resources than commercially driven studies, another important factor in recruitment.

For example, the Third International Stroke Trial (IST-3), a recently completed trial which will significantly change clinical practice, suffered a difficult initial recruitment period (29). This trial tested the hypothesis that the administration of tPA within 6 hours of symptom onset increases the proportion of people alive and independent at 6 months. Began in May 2005, the study finished its recruitment phase at the end of July 2011 and the results, based

on more than 3000 randomised patients, have been recently reported (29). In 2007, it became clear that recruitment of 6000 patients by 2009 was not realistic. An extension to funding permitted recruitment to continue until mid-2011. Then modified protocol with a revised sample size of 3035 patients still had an acceptable power to detect a 3% absolute difference in the primary outcome (30).

One issue of importance in testing the efficacy of tPA beyond 4.5 hours is the possibility of a reduced size of the target population. The effect of stroke prevention campaigns, such as FAST (Face, Arm, Speech, Time) used in 2007 by the National Stroke Foundation in Australia and similar campaigns in many countries (31), could have prompted people to get to hospital earlier after stroke onset, thus diminishing the later arrival sample. However, this explanation is not supported in our population when a comparison was made between our 2010 data and historical arrival. Hence, data from the North East Melbourne Stroke Incidence Study (NEMESIS) conducted between 1997 and 1998 indicated that 34% of stroke patients arrived at hospital within 3 hours, 40% within 4 hours, 45% within 6 hours and 53% within 12 hours (32). Similarly, the annual evaluation of Victorian Stroke Services reported in 2002 that 25% of acute stroke patient arrived at hospital within 2 hours of stroke onset and 41% arrived within 6 hours (33). Confirming this finding, a recent systematic review has shown that a number of prevention campaigns in Canada and the USA have resulted in increases in symptom awareness and awareness of the need for emergency response but found no increased use of emergency response, shorter time to arrival or increased use of thrombolysis (34).

EXTEND is one of the few trials using a combination of clinical and imaging inclusion criteria. Based on the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) results (35), imaging parameters such as optimised perfusion weighted imaging/diffusion weighted

imaging ratio have been chosen to select an enriched population of patients in whom there is a greater chance of therapeutic responsiveness. Importantly, EXTEND seems most likely to be valuable for the approximately 25% of ischaemic stroke patients in whom stroke occurs during sleep (36-38). Currently they are ineligible for thrombolysis because of the uncertain time of stroke onset. Since these represent a large proportion of the EXTEND target population (70.5%), the imaging data may support the current concept that many such strokes occur around the time of awakening (37,39-41).

Like many trials involving imaging parameters as an inclusion criterion, EXTEND is exposed to MRI availability issues. A large number of potential patients arrived in the ED outside available MRI hours which are restricted in most Australian centres. Indeed, 13 of the 17 patients who could have been screened for randomisation at Austin Health arrived outside the 8:30 am to 4:30 pm Monday to Friday time frame. MRI access undeniably plays a crucial role in EXTEND recruitment. By increasing MRI availability to 8:00 am to 6:00 pm on week days, 12 more patients could have been screened. An extension of 2 hours of daily MRI availability would have increased cohort recruitment from four to 12 (when assuming every patient agreed to participate) or an increase of 300%.

Speed and simplicity in establishing imaging parameters is an important feature of patient assessment for trial eligibility. In EXTEND, an automated MRI analysis software is used which was developed by the Stanford imaging group (RAPID). The system allows rapid, standardised and reproducible volumetric analysis of mismatch and has been proved to be useful for patient selection in acute stroke trials (42). As CTP scanning has been validated as an alternative modality to determine penumbral mismatch (43,44), RAPID has been modified to allow the use of CTP scans. Interestingly, CTP scan was the imaging selection technique

used in the recently completed study of tenecteplase compared to tPA in ischaemic stroke and this allowed reasonably rapid recruitment to be achieved (45).

Logically, the principal investigators of EXTEND have recently added CTP scanning as an additional means to identify patients with a significant mismatch. CTP scanning is routinely performed as standard care in most major hospital centres, and is more readily available than MRI, particularly outside business hours. In addition, CTP scan use has fewer restrictions (for example, pacemaker use) compared to MRI. This protocol change will allow more patients to be screened and thereby identify more patients eligible for randomisation to treatment based on penumbral mismatch criteria. Indeed, with CTP scanning available 24 hours each day, all 13 patients who arrived outside Austin Health MRI opening hours could have been recruited and potentially randomised using the EXTEND inclusion and exclusion criteria. Clearly, 24 hour access to imaging facilities is likely to become even more necessary for routine stroke management in future years as the selection of patients and treatment strategies become more sophisticated.

References

1. The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis.* 2008;25:457-507.
2. Strong K, Mathers C, Bonita R. Preventing stroke: saving lives around the world. *Lancet Neurol.* 2007;6:182-7.
3. Rosamond W, Flegal K, Friday G et al. Heart Disease and stroke statistics - 2007 update: a report from American Heart Stroke Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2007;115:69-71.

4. Rothwell PM, Coull AJ, Silver LE et al. Population-based study of event-rate, incidence, case fatality, and mortality for all acute vascular events in all arterial territories. *Lancet*. 2005;366:1773-83.
5. Hacke W, Kaste M, Bluhmki E et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317-29.
6. Walter S, Kostopoulos P, Haass A et al. Bringing the hospital to the patient: first treatment of stroke patients at the emergency site. *PLoS ONE* 2010;5:e13758.
7. Khaja AM, Grotta JC. Established treatments for acute ischaemic stroke. *Lancet* 2007;369:319-30.
8. Eriksson M, Jonsson F, Appelros P et al. Dissemination of thrombolysis for acute ischemic stroke across a nation: experiences from the Swedish stroke register, 2003 to 2008. *Stroke* 2010;41:1115-22.
9. Kleindorfer D, Xu Y, Moomaw CJ, Khatri P, Adeoye O, Hornung R. US geographic distribution of rt-PA utilization by hospital for acute ischemic stroke. *Stroke* 2009;40:3580-4.
10. Iguchi Y, Kimura K, Sone K et al. Stroke Incidence and Usage Rate of Thrombolysis in A Japanese Urban City: The Kurashiki Stroke Registry. *J Stroke Cerebrovasc Dis*. In Press, Corrected Proof, Available online 1 November 2011
11. Duffy BK, Phillips PA, Davis SM, Donnan GA, Vedadhaghi ME. Evidence-based care and outcomes of acute stroke managed in hospitals specialty units. *Med J Aust* 2003;178:318-23.
12. Kleindorfer D, Lindsell CJ, Brass L, Koroshetz W, Broderick JP. US estimates of recombinant tissue plasminogen activator use: ICD-9 codes substantially underestimate. *Stroke*. 2008;39:924-8

13. Albers GW, Olivot JM. Intravenous alteplase for ischaemic stroke. *Lancet* 2007;369:249-50.
14. Minnerup J, Wersching H, Ringelstein EB et al. Impact of the extended thrombolysis time window on the proportion of recombinant tissue-type plasminogen activator-treated stroke patients and on door-to-needle time. *Stroke* 2011;42:2838-43.
15. Dalloz MA, Bottin L, Muresan IP et al. Thrombolysis rate and impact of a stroke code: A French hospital experience and a systematic review. *J Neurol Sci.* 2012;314:120-5.
16. 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;333:1581-7.
17. Furlan AJ, Eyding D, Albers GW et al. Dose escalation of desmoteplase for acute ischemic stroke (DEDAS): evidence of safety and efficacy 3 to 9 hours after stroke onset. *Stroke* 2006;37:1227-31.
18. Hacke W, Kaste M, Fieschi C et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995;274:1017-25
19. Hacke W, Kaste M, Fieschi C et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASSII). *Lancet* 1998;352:1245-51.
20. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant Tissue-Type Plasminogen Activator (Alteplase) for Ischemic Stroke 3 to 5 Hours After Symptom Onset. The ATLANTIS Study: A Randomized Controlled Trial. *JAMA* 1999;282:2019-26.
21. Clark WM, Albers GW, Madden KP, Hamilton S. The rt-PA (alteplase) 0- to 6- hour acute stroke trial, part A (A0267g): results of a double-blind, placebo-controlled, multicenter study. *Stroke* 2000;31:811-6.

22. Hacke W, Donnan G, Fieschi C et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS and NINDS rt-PA stroke trials. *Lancet* 2004;363:768-74.
23. Ma H, Parsons MW, Christensen S et al. A multicentre, randomized, double-blinded, placebo-controlled Phase III study to investigate EXtending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND). *Int J Stroke*. 2012;7:74-80.
24. Lloyd G, Dean CM, Ada L. Issues in recruiting community-dwelling stroke survivors to clinical trials: The AMBULATE trial. *Contemp Clin Trials* 2010;31:289-92.
25. Cumberland Consensus Working Group. Cheeran B, Cohen L, Dobkin B et al. The future of restorative neurosciences in stroke: driving the translational research pipelines from basic science to rehabilitation of people after stroke. *Neurorehabil Neural Repair* 2009;23:97-107.
26. Alexandrov AV. Slow recruitment in clinical trials: failure is not an option! *Int J Stroke*. 2006;1:160.
27. Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G. A very early rehabilitation trial for stroke (AVERT): phase II safety and feasibility. *Stroke* 2008;39:390-6.
28. Gul RB, Ali PA. Clinical trials: the challenge of recruitment and retention of participants. *J Clin Nurs*. 2010;19:227-33.
29. IST-3 collaborative group. 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;379:2352-63.
30. Sandercock P, Lindley R, Wardlaw J et al. Update on the third international stroke trial (IST-3) of thrombolysis for acute ischaemic stroke and baseline features of the 3035 patients recruited. *Trials* 2011;12:252.

31. Bray JE, O'Connell B, Gilligan A, Livingston PM, Bladin C. Is FAST stroke smart? Do the content and language used in awareness campaigns describe the experience of stroke symptoms? *Int J Stroke* 2010;5:440-6.
32. Gilligan AK, Thrift AG, Sturm JW, Dewey HM, Macdonell RA, Donnan GA. Stroke Units, Tissue Plasminogen Activator, Aspirin and Neuroprotection: Which Stroke Intervention Could Provide the Greatest Community Benefit? *Cerebrovasc Dis* 2005;20:239-44.
33. Public Health Division, National Stroke Foundation, Australia. Stroke Care Outcomes: Providing Effective Services. SCOPES Report October 2002.
34. Lecouturier J, Rodgers H, Murtagh MJ, White M, Ford GA, Thomson RG. Systematic review of mass media interventions designed to improve public recognition of stroke symptoms, emergency response and early treatment. *BMC Public Health* 2010;10:784.
35. Davis SM, Donnan GA, Parsons MW et al. Effects of alteplase beyond 3h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol* 2008;7:299-309.
36. Nadeau JO, Fang J, Kapral MK, Silver FL, Hill MD. Outcome after stroke upon awakening. *Can. J. Neurol. Sci.* 2005;32:232-6.
37. Barreto AD, Martin-Schild S, Halleivi H et al. Thrombolytic therapy for patients who wake-up with stroke. *Stroke* 2009;40:827-32.
38. Fink JN, Kumar S, Horkan C et al. The stroke patient who woke up: clinical and radiological features, including diffusion and perfusion MRI. *Stroke* 2002;33:988-93.
39. Elliott WJ. Circadian variation in the timing of stroke onset: a meta-analysis. *Stroke* 1998;29:992-6.
40. Silva GS, Lima FO, Camargo EC et al. Wake-up stroke: clinical and neuroimaging characteristics. *Cerebrovasc Dis* 2010;29:336-42.

41. Huisa BN, Raman R, Ernstrom K et al. Alberta stroke program early CT score (aspects) in patients with wake-up stroke. *J Stroke Cerebrovasc Dis* 2010;19:475–9.
42. Lansberg MG, Lee J, Christensen S et al. RAPID Automated Patient Selection for Reperfusion Therapy. A pooled analysis of the echoplanar imaging thrombolytic evaluation trial (EPITHET) and the diffusion and perfusion imaging evaluation for understanding stroke evolution (DEFUSE) study. *Stroke* 2011;42:1608-14.
43. Bivard A, McElduff P, Spratt N, Levi C, Parsons M. Defining the extent of irreversible brain ischemia using perfusion computed tomography. *Cerebrovasc Dis.* 2011;31:238-45.
44. Kamalian S, Kamalian S, Maas MB et al. CT Cerebral Blood Flow Maps Optimally Correlate With Admission Diffusion-Weighted Imaging in Acute Stroke but Thresholds Vary by Postprocessing Platform. *Stroke* 2011;42:1923-8.
45. Parsons M, Spratt N, Bivard A et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med.* 2012;366:1099-107.

Figure legends

Fig. 1. Proportion of wake-up stroke (WUS) and patients presenting between 4.5–9 hours (H) after stroke onset in the EXTEND target population.

EXTEND = Extending the time for Thrombolysis in Emergency Neurological Deficits trial.

Fig. 2. Proportion of patients arriving during or outside office hours in the EXTEND target population.

EXTEND = Extending the time for Thrombolysis in Emergency Neurological Deficits trial.

Fig. 3. Proportion of patients with or without exclusion criteria in the EXTEND target population.

EXTEND = Extending the time for Thrombolysis in Emergency Neurological Deficits trial.

Fig. 4. EXTEND exclusion criteria identified in patients arriving between 4.5–9 hours after stroke onset and wake-up stroke.

EXTEND = Extending the time for Thrombolysis in Emergency Neurological Deficits trial, ICH = intracerebral haemorrhage, INR = International Normalised Ratio, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, tPA = tissue plasminogen activator.

Fig. 5. Flow diagram of patient disposition (and percentages of total admission) through the recruitment process.

WUS = wake-up stroke.

Table 1. EXTEND inclusion criteria. Patients meeting only the general inclusion criteria are recruited for an observational cohort, patients meeting both general and MRI inclusion criteria are recruited to the randomised controlled trials.

General inclusion criteria

1. Participants presenting with ischaemic stroke
2. Participant, family member or legally responsible person has given informed consent
3. Participant is 18 years old or over
4. Treatment onset can commence after 4.5 hours and up to and including 9 hours after stroke onset
5. Participants who wake up with stroke may be included if neurological and other exclusion criteria are satisfied. (Wake-up stroke is defined as having no symptoms of stroke at sleep onset but symptoms upon waking. The inclusion time window for wake-up stroke is less than or equal to 9 hours from the mid-point between going to bed and waking with symptoms)
6. NIHSS score of equal to or between 4 and 26 with clinical signs of hemispheric infarction

MRI inclusion criteria

7. Penumbral imaging – using a Tmax >6 second delay
 - PWI volume to DWI volume ratio greater than 1.2
 - DWI lesion less than or equal to 70 ml
 - PWI–DWI absolute difference of greater than 10 ml

DWI = diffusion weighted imaging, EXTEND = Extending the time for Thrombolysis in Emergency Neurological Deficits trial, NIHSS = National Institutes of Health Stroke Scale, PWI = perfusion weighted imaging, Tmax = time to maximum.

Table 2 EXTEND exclusion criteria

Exclusion criteria

1. ICH identified by CT scan or MRI
2. Rapidly improving symptoms
3. Pre-stroke mRS score of ≥ 2
4. Contra-indication to imaging with MRI contrast agents
5. Infarct core greater than one-third of MCA territory
6. Participation in investigational study in the past 30 days
7. Any terminal illness such as the patient would not be expected to survive more than 1 year
8. Hazardous conditions for tPA for example, haemolytic uremic syndrome, thrombotic thrombocytopenic purpura
9. Pregnant women (clinically evident)
10. Previous stroke within the last 3 months
11. Recent ICH, subarachnoid haemorrhage, AV malformation, aneurysm, cerebral neoplasm
12. Oral anticoagulants and INR >1.6
13. Heparin use in past 48 hours (except low dose) and prolonged APTT
14. Glycoprotein IIb-IIIa inhibitors in past 72 hours. Clopidogrel and/or low dose aspirin permitted
15. Clinically significant hypoglycaemia
16. Uncontrolled hypertension (BP >185 mmHg systolic or >110 mmHg diastolic)
17. Hereditary or acquired haemorrhagic diathesis
18. Gastrointestinal or urinary bleeding in the past 21 days
19. Major surgery in the past 14 days which poses risk
20. Exposure to a thrombolytic agent in the previous 72 hours

APTT = activated partial thromboplastin time, AV = arteriovenous, BP = blood pressure, EXTEND = Extending the time for Thrombolysis in Emergency Neurological Deficits trial, ICH = intracerebral haemorrhage, INR = International Normalised Ratio, MCA = middle cerebral artery, mRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, tPA = tissue plasminogen activator.

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Dagonnier, M;Howells, DW;Donnan, GA;Dewey, HM

Title:

Recruitment to trials of late thrombolysis: Lessons from the EXTEND study

Date:

2014-07-01

Citation:

Dagonnier, M., Howells, D. W., Donnan, G. A. & Dewey, H. M. (2014). Recruitment to trials of late thrombolysis: Lessons from the EXTEND study. JOURNAL OF CLINICAL NEUROSCIENCE, 21 (7), pp.1215-1219. <https://doi.org/10.1016/j.jocn.2013.10.033>.

Persistent Link:

<http://hdl.handle.net/11343/44016>