

Does the Addition of Non-Approved Inclusion and Exclusion Criteria for rtPA Impact Treatment Rates? Findings in Australia, the UK, and the USA

Craig, Louise E.; Middleton, Sandy; Hamilton, Helen; Cudlip, Fern; Swatzell, Victoria; Alexandrov, Andrei V.; Lightbody, Elizabeth; Watkins, Dame Caroline; Philip, Sheeba; Cadilhac, Dominique A.; McInnes, Elizabeth; Dale, Simeon; Alexandrov, Anne W.

Published in:
Interventional Neurology

DOI:
[10.1159/000493020](https://doi.org/10.1159/000493020)

Published: 01/01/2019

Document Version:
Peer reviewed version

Licence:
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Recommended citation(APA):

Craig, L. E., Middleton, S., Hamilton, H., Cudlip, F., Swatzell, V., Alexandrov, A. V., Lightbody, E., Watkins, D. C., Philip, S., Cadilhac, D. A., McInnes, E., Dale, S., & Alexandrov, A. W. (2019). Does the Addition of Non-Approved Inclusion and Exclusion Criteria for rtPA Impact Treatment Rates? Findings in Australia, the UK, and the USA. *Interventional Neurology*, 8(1), 1-12. <https://doi.org/10.1159/000493020>

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1 **Do the Addition of Non-Approved Inclusion and Exclusion Criteria for rtPA**
2 **Impact Treatment Rates? Findings in Australia, the United Kingdom and the**
3 **United States of America**

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99 **Abstract**

100

101 **Background:** Strict criteria for recombinant tissue plasminogen activator (rtPA) eligibility are
102 stipulated on licences for use in ischaemic stroke, however, practitioners may also add non-standard
103 rtPA criteria. We examined eligibility criteria variation in 3 English-speaking countries including use
104 of non-standard criteria, in relation to rtPA treatment rates.

105

106 **Methods:** Surveys were mailed to 566 eligible hospitals in Australia (AUS), United Kingdom (UK) and
107 the United States (USA). Criteria were pre-classified as standard (approved indication and
108 contraindications) or non-standard (approved warning or researcher 'decoy'). Percentage for
109 criterion selection was calculated/compared; linear regression was used to assess the association
110 between use of non-standard criteria and rtPA treatment rates, and to identify factors associated
111 with addition of non-standard criteria.

112

113 **Results:** Response rates were 74% AUS, 65% UK, and 68% USA; mean rtPA treatment rates were
114 8.7% AUS, 12.7% UK and 8.7% USA. Median percentage of non-standard inclusions was 33% (all 3
115 countries) and included National Institutes of Health Stroke Scale (NIHSS) scores >4, computed
116 tomography (CT) angiography documented occlusion, and favourable CT perfusion. Median
117 percentage of non-standard exclusions was 25% AUS, 28% UK, and 60% USA, and included
118 depressed consciousness, NIHSS>25, and use of antihypertensive infusions. No AUS or UK sites
119 selected 100% of standard exclusions.

120

121 **Conclusions:** Non-standard criteria for rtPA eligibility was evident in all three countries and could, in
122 part, explain comparably low use of rtPA. Differences in the use of standard criteria may signify
123 practitioner intolerance for those derived from original efficacy studies that are no longer relevant.

124

125

126 **Introduction**

127 Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) has been shown to
128 be safe and effective, and is one of the few evidence based treatments for acute ischaemic stroke.[1-
129 5] Currently, the percentage of patients with ischaemic stroke receiving rtPA varies globally, with 7%
130 treated in the stroke centre certified United States of America (USA) hospitals,[6] 7% in Australia
131 (AUS)[7] and 12% treated in the United Kingdom (UK) .[8] The narrow time frame for therapeutic
132 administration, which in the UK and AUS is within 4.5 hours of symptom onset and in the USA is
133 within 3 (approved indication) or 4.5 (guidelines) hours, is one main factor for low treatment rates.
134 However, improved rtPA treatment rates are possible when internal hospital organisational factors
135 are addressed,[9-12] and when regional stroke systems are operationalised to support patients with
136 acute stroke.[13-16]

137
138 Eligibility criteria for rtPA are largely derived from clinical trials with the aim of producing similar
139 beneficial outcomes in routine practice. However, the addition of local or “site-specific” (non-
140 standard) eligibility criteria may result in otherwise eligible patients not receiving rtPA. There is a
141 growing evidence base on the additional reasons for low rtPA treatment rates, including the fit
142 between eligibility criteria and actual patient selection practices.[17-19] In particular, many of the
143 criteria used in clinical trials may no longer be relevant given that the drug was first approved over
144 20 years ago.[20-22] Mounting evidence from pooled analyses, observational studies and clinical
145 trials, some studying an extended time window of 4.5hours and practices less adherent with
146 standard criteria, suggests that rtPA can be delivered safely to patients previously deemed
147 ineligible.[22-31]

148
149 The eligibility criteria for rtPA administration varies between countries.[32-35] The European and
150 Australian guidelines share many similarities, but these differ substantially from the USA guidelines,
151 and the USA guidelines vary significantly from the drug’s approved indications and contraindications
152 Varying criteria between national drug regulatory bodies, professional organisations, and individual
153 hospital protocols challenges international consensus on what constitutes patient eligibility for
154 treatment. There is an urgent need to understand these issues, including the addition of non-
155 standard criteria for selecting patients eligible for rtPA treatment. The aims of this study were to: 1)
156 describe the criteria for patient selection for rtPA treatment by country; 2) to determine the
157 association between the use of non-standard criteria and rtPA treatment rates in three different
158 countries; and, 3) to identify the organisational factors associated with the addition of non-standard
159 criteria.

160

161

162 **Methods**

163 Ethics approval was obtained from the following institutions for the conduct of this study: Eden
164 Hospital, Castro Valley California (USA coordinating centre), the University of Central Lancashire (UK
165 coordinating centre), and the Australian Catholic University (Australian, and overall international
166 coordinating centre). We undertook a cross-sectional survey of rtPA eligibility and treatment
167 practices within hospitals in Australia, the UK and the USA that routinely used rtPA for management
168 of acute stroke patients. The survey was conducted between 2013-2016 and analysed in
169 2017.

170

171 *Hospital selection*

172 All hospitals in AUS and in the UK known to provide rtPA for acute ischaemic stroke were eligible for
173 the study and were identified via the Stroke Foundation Organisational Survey[36] and The Sentinel
174 Stroke National Audit Programme (SSNAP), respectively. In the USA, stroke centre hospitals were
175 included based on the following inclusion criteria: 1) nationally certified by The Joint Commission for
176 a minimum of 12 months at the time of survey mailing; 2) use of an organised acute stroke team in
177 the approach to emergency diagnosis and treatment; and, 3) formal identification by policy and
178 procedure of eligibility criteria for rtPA treatment.

179

180 *Survey distribution*

181 Within each hospital, one eligible staff member was identified to complete the survey: the Stroke
182 Unit Co-ordinator in AUS and the USA and the SSNAP lead contact for the Trust in the UK Identified
183 staff who were approached by mail (AUS and USA) or email (UK) with a letter inviting them to
184 participate in the survey along with a copy of the questionnaire. Prior to this invitation, an advanced
185 letter was sent to notify potential participants of the pending survey as a response aiding
186 strategy.[37] Participation was voluntary and consent was implied by completion and return of the
187 questionnaire. Completed questionnaires were returned via post, fax or completed and returned
188 electronically. Non-respondents were followed-up by email or phone at six weeks and eight weeks in
189 AUS and the UK. In the USA follow-up consisted of a second and third mail out at eight and 16 weeks
190 from the initial mail out date.

191

192 *Survey content and development*

193 The survey was originally designed for study in the USA and included both standard criteria for rtPA
194 use in stroke patients (criteria stipulated by the USA rtPA approved indications and contraindications
195 and/or guidelines) and non-standard criteria (i.e. decoys derived from interviews with both expert
196 users and community neurologists in the USA). This survey was then tailored for use in AUS and UK
197 by adding criteria specified by the relevant country: i) manufacturer, ii) drug regulatory body, and iii)
198 stroke clinical guidelines (referred collectively as 'practice recommendations' hereafter). The
199 Australian and UK version of the survey was pre-tested with a panel of experts (Neurologists, Stroke
200 Clinicians and Stroke Nurses) to identify any ambiguous questions and to recommend further decoy
201 criteria. All three versions of the surveys consisted of two main sections; one section listed all the
202 inclusion criteria, and one section listed all the exclusion criteria. Participants were instructed to
203 select all of the criteria that were used at their hospital to assess if patients are eligible for rtPA.
204 Additional space was provided for participants to write in criteria that were not included on the
205 questionnaire. Information was also collected on organisational factors which included type of
206 stroke service (tertiary / non-tertiary referral centre), number of beds, number of ischaemic stroke
207 admissions in the last 12 months, rtPA treatments in the last 12 months, door-to-needle time and
208 who was involved in the selection and decision-making process for rtPA.

209

210 **Data Analysis**

211 Descriptive analyses were used to summarise the self-reported characteristics of the stroke services
212 by country. Criteria for patient selection for rtPA were pre-classified as either "standard" (an
213 inclusion or exclusion specified by country practice recommendations) or "non-standard" (warnings
214 specified by country practice recommendations or decoy criteria developed by the researchers). To
215 determine criteria being used, the percentage of respondents that selected each criterion was
216 calculated. For each hospital, the proportion of standard and nonstandard criteria of the total
217 criteria was calculated. The proportion calculated for each hospital was summarised for each
218 country and reported as a median percentage. Criteria added by respondents were independently
219 reviewed by study investigators (LC, HH, AA), and classified to existing groups if meanings were
220 similar or classified as non-standard criteria if meanings were unique. Treatment rates were
221 calculated for each hospital using the number of annual rtPA treatments reported, divided by the
222 number of annual ischemic stroke admissions, multiplied by 100. Independent Student *t*-tests and
223 one-way analysis of variance (ANOVA) were undertaken to examine the associations between pre-
224 specified stroke service variables (hospital setting [tertiary/non-tertiary] and door to needle times)
225 and rtPA treatment rates in each country. Linear regression analyses were conducted for each of
226 the countries to assess associations between non-standard criteria and rtPA treatment rates. Linear

227 regression models were developed using preselected variables to identify organisational factors
228 associated with the addition of non-standard criteria in each country. Analyses were conducted with
229 Stata version 14.

230

231 **Results**

232 The response rates per country were 68% (AUS 74% (63/85), UK 65% (93/144) and USA 68%
233 (229/337). Tertiary hospital staff made up 39% of respondents overall (AUS 46%; UK 53%; USA 29%),
234 with 38% of AUS respondents and 69% of USA respondents reporting comprehensive stroke centre
235 (CSC) capabilities (CSC status was not reported on the UK survey) (Supplement Table A). Decision
236 makers for treatment with rtPA in AUS and the USA were most commonly neurologists (84% and
237 87%, respectively), whilst the majority of UK respondents selected stroke (usually geriatrician)
238 physicians (99%). Interestingly, 31% of USA centres would only accept an rtPA order from a
239 neurologist. Telemedicine was not used in 68% and 39% of AUS and UK respondents respectively
240 (not collected on USA survey) (Supplement Table A).

241

242 ***Differences in rtPA Treatment Rates***

243 Of responding stroke centres, 60 (95%) AUS, 77 (83%) UK, and 184 (80%) USA centres included both
244 their annual ischaemic stroke patient volumes and their annual rtPA treatment volumes enabling
245 calculation of rtPA treatment rates. Mean rtPA treatment rate for Australia, UK and USA were 8.7%
246 (SD=5.8), 12.7% (SD=4.7) and 8.7% (SD=6.4), respectively. Supplement Table B shows differences in
247 rtPA treatment rates by tertiary care designation and door-to-needle times. Rates for rtPA
248 treatments were consistently higher for tertiary than non-tertiary hospitals and increased with
249 shorter door-to-needle time for all three countries, although differences in mean rates were only
250 significantly different for USA (F 7.64; $p < 0.001$).

251 ***Selection of Inclusion Criteria for rtPA Treatment***

252 The median percentage of standard criteria selected by USA (50%; IQR 25) respondents was less
253 than that selected by AUS (100%; IQR 33) and UK (100%; IQR 0) respondents. The median
254 percentage of non-standard criteria selected by respondents from all three countries was 33%.

255

256 Table 1 lists standard and non-standard inclusion and exclusion criteria and their rates of selection
257 by country. The standard USA approved inclusion criterion, '*Ability to start rtPA within 3 hours from*
258 *symptom onset*' was selected by almost a quarter of USA respondents. The non-standard criterion
259 for limiting inclusion to patients with National Institutes of Health Stroke Scale scores greater than 4
260 points was selected by about half of respondents from AUS (49%) and the UK (51%), and 35% of USA

261 respondents. The non-standard criterion for a favourable computed tomographic (CT) perfusion
262 (CTP) scan in patients inside the window for rtPA treatment was selected by 22% of AUS and 19% of
263 USA respondents, whereas only 11% of UK respondents selected this criterion. Additionally, 21%
264 and 26% of AUS and USA respondents respectively required evidence of occlusion on CT angiography
265 (CTA) as an rtPA non-standard inclusion criterion, compared to 16% of UK respondents.

266

267 ***Selection of Exclusion Criteria for rtPA Treatment***

268 The median percentage of standard exclusion criteria selected by USA (82%; IQR 18) respondents
269 was higher than that selected by AUS (66%; IQR 24) and UK (64%; IQR 25) respondents. The median
270 percentage of non-standard exclusions selected by USA respondents (60%; IQR 60) was again higher
271 than that selected by AUS (25%; IQR 19) and UK (28%; IQR 17) respondents.

272

273 There were no respondents within AUS or the UK that selected all their country's standard exclusion
274 criteria, and all AUS and UK respondents added non-standard exclusion criteria. Both "*NIHSS > 25*"
275 and "*altered level of consciousness (obtunded, stuporous, or comatose)*" were selected by 62% and
276 42% of AUS and UK respondents respectively, whereas 31% of USA respondents reported that their
277 hospital excluded patients with NIHSS > 25, and 7% of USA respondents' hospitals excluded patients
278 with altered level of consciousness. Additionally, 29%, 24% and 7% of AUS, UK and USA respondents
279 indicated that their hospital excludes patients from rtPA treatment if they require a continuous IV
280 infusion of an antihypertensive agent. Patients with large vessel occlusion (LVO) were considered an
281 exclusion for rtPA treatment by 14% of USA respondents, in favour of endovascular management,
282 whereas 1.6% and 8.6% of AUS and UK respondents respectively reported that their hospitals
283 exclude LVO from rtPA treatment in favour of endovascular treatment. Age greater than 80 years
284 was listed as an exclusion by 13% and 16% of AUS and USA respondents respectively, compared to
285 only 3% of UK respondents, regardless of whether treating within the 3 or 4.5-hour treatment
286 window.

287

288 ***Relationship of Non-Standard Criteria to rtPA Treatment***

289 As the number of non-standard inclusions and exclusions increased, rtPA treatment rates slightly
290 decreased in all three countries. As the number of non-standard criteria increased by one the rtPA
291 rate decreased by 0.48% ($p=0.05$), 0.31% ($p=0.07$) and 0.16% ($p=0.13$) for AUS, UK and the USA,
292 respectively.

293

294 ***Association Between Factors and the Addition of Non-Standard Criteria***

295 Factors significantly associated with the addition of non-standard criteria in the USA were as follows:
296 non-tertiary hospital setting (-1.72 [95%CI -3.25, -0.20]); p-value=0.03); average door-to-needle time
297 greater than 60 minutes (3.57 [95%CI -0.38, 6.75]; p-value=0.023) and adherence to 3-hour
298 treatment window (-2.44 [95%CI -4.30, -0.60]); p-value=0.01). No factors were significantly
299 associated with the addition of non-standard criteria in AUS or in the UK (Supplement Table C).

300

301 **Discussion**

302 Our study found that clinicians commonly develop and use non-standard criteria for selection of rtPA
303 eligible patients. Importantly, both AUS and the UK have greater numbers of standard criteria
304 compared to the USA, yet participants from these countries use more non-standard criteria than in
305 the USA. The use of non-standard exclusion criteria has been investigated in other studies, however,
306 the aims of most of these studies were to identify the impact of non-standard eligibility criteria on
307 early clinical outcomes such as rates of symptomatic intracerebral haemorrhage (sICH).[20-23,38]
308 To the best of our knowledge, our study appears to be the only one examining clinicians' formal
309 protocol additions of non-standard criteria in relation to rtPA treatment rates.

310

311 There were a number of differences in the criteria between countries relating to the use of both
312 standard and non-standard exclusion criteria. Differences in use of standard criteria between
313 countries could signify clinical uncertainty, conflicting research evidence, or perhaps an intolerance
314 for continued use of criteria that supported efficacy studies of rtPA in acute ischemic stroke but may
315 not be relevant outside a phase III clinical trial. For example, both severe neurologic disability and
316 blood glucose limits were considered warnings but not contraindications on the former (prior to
317 February 2015) [39] USA label for rtPA, whereas the Australian and UK labels continue to stipulate
318 specific limits from which to exclude rtPA treatment. Interestingly, the February 2015 USA Food and
319 Drug Administration (FDA) rtPA approved label [39] removed severe neurologic disability as a
320 precaution, based on findings from the original National Institute of Neurological Disorders and
321 Stroke rtPA Stroke Study that showed significant improvement in severe disability patients treated
322 with rtPA compared to placebo.[40] Similarly, the 2015 USA FDA approved label [39] no longer cites
323 blood glucose values as warnings, as these are easily monitored and managed in both the pre-
324 hospital and emergency department settings.

325

326 The use of some standard exclusions was fewer than expected in both AUS and the UK. For example,
327 less than 25% of participants in these countries selected the standard exclusion, *patients with any*
328 *history of prior stroke and concomitant diabetes*. Although the use of rtPA has not been approved in

329 Europe for these patients, registry studies have shown that while this criterion may have been
330 important in the ECASS-3 efficacy study,[2] it may not be relevant to real-world practice and does
331 not jeopardise the safe treatment of patients with rtPA.[41-42] While trial methods do provide a
332 degree of certainty about what results to expect in a similar population, use of approved therapies in
333 the real world often calls for less exclusivity.[43]

334

335 It has been recognised internationally that selection criteria may be too restrictive and some have
336 expressed concerns that the evidence underpinning the need to include certain criteria is not
337 robust.[20-28,43-45] The 2015 USA FDA labeling requirements for prescription drugs, commonly
338 referred to as the 'Physician Labelling Rule' (PLR), state 'No implied claims or suggestions of drug use
339 may be made if there is inadequate evidence of safety or a lack of substantial evidence of
340 effectiveness,[46] meaning that unless there is high level evidence to support a safety concern, it
341 should not be considered a contraindication. The USA FDA's PLR requirements significantly reduced
342 the number of USA exclusion criteria to seven in 2015, with previous stroke, seizure at onset, and
343 history of intracranial haemorrhage removed; additionally, blood pressure cut off levels, as well as
344 lab values for bleeding diathesis were also removed in favour of relying on evidence-based
345 guidelines to set these values.[39] The 2015 USA FDA label also removed precautions for severe
346 neurologic deficit, major early infarct signs, minor neurologic deficit, and rapidly improving
347 symptoms.[39] Interestingly, the majority of the USA criteria that were removed, currently remain
348 on the European and Australian labels, and we believe that this calls for a more thorough evaluation
349 of whether these criteria are truly valid perhaps using the processes established by The Re-
350 examining Acute Eligibility for Thrombolysis (TREAT) Task Force is comprised members of the original
351 NINDS rtPA Stroke Trial Steering Committee,[47] especially with sICH rates from more recent studies
352 and registries commonly at less than 3%.[2,48-52] The investigators of a recent study which aimed to
353 assess whether adherence to drug labels is associated with efficacious patient outcomes concluded
354 that product labels need to be revised, finding that adherence with product labels is highest with
355 less efficacious interventions.[53]

356

357 **Limitations**

358 This study carries the limitations of survey research such as the risk of response and recall bias. First,
359 we assume that findings submitted are truthful and accurately reflect the practice at the
360 participating stroke centres, although this may not be the case. We also acknowledge that some
361 items such as aortic arch dissection were not listed as criteria in the questionnaire for participants to
362 select. Additionally, surveys do not provide the meaning or context behind a response. Therefore,

363 we are limited in our ability to provide an understanding of why and how clinicians make certain
364 decisions including their areas of clinical or research uncertainty.[54] Lastly, although this
365 questionnaire was personally addressed to Stroke Unit Coordinators, a variety of professional groups
366 responded; while this was anticipated and encouraged by our instructions to '*collaborate with*
367 *colleagues, who are involved in the decision-making and administration of rtPA for stroke patients,*' it
368 does potentially introduce a source of differential error and measurement error. Furthermore, this is
369 a highly dynamic field, with new imaging criteria re-defining reperfusion strategies at different
370 time points.[55,56] Therefore, it would be worthwhile to repeat this study as the reperfusion
371 paradigm shifts.

372

373 **Strengths**

374 This research provides novel data about rtPA international administration practices and the
375 differences in the use of selection criteria in three different countries, two with similar healthcare
376 systems (AUS/UK), and the USA with a largely private health system. The survey had a reasonable
377 response rate for all three countries which adds external validity to the findings, and our survey tools
378 were extensively pre-tested with experts contributing face validity to our methods.

379

380 **Conclusion**

381 This study provides novel, and somewhat provocative data about the criteria used to select patients
382 for rtPA across three English-speaking countries, in particular, the relatively common use of non-
383 standard criteria for rtPA eligibility which may contribute in part, to low rtPA treatment rates.

384

385 **Consent for publication**

386 Not applicable.

387 **Availability of data and material**

388 All data generated or analysed during this study are included in this published article (and its
389 supplementary information files).

390 **Competing interests**

391 Anne W. Alexandrov and Andrei V. Alexandrov are members of the Genentech Speakers Bureau. All
392 other authors declare that there are no competing interests.

393 **Funding**

394 This project was supported by an infrastructure grant provided by the Australian Catholic University
395 to support the International Stroke Research Collaboration.

396 **Author contributions**

397 AWA, FC & VS conceived the study. AWA, AVA, LEC, SM, DC & CW designed the study. LEC, HH and
398 CEL conducted all analyses. The paper was jointly written and reviewed by all authors.

399 **Acknowledgements**

400 Not applicable.

401 **Authors' Information Section**

402 DC was supported by a fellowship from the National Health and Medical Research Council (NHMRC;
403 1063761 co-funded by National Heart Foundation)

404

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Table 1 **Reported rt-PA eligibility criteria by country**

INCLUSION CRITERIA	AUS	UK	USA
	N=63	N=93	N=229
<i>Standard all (n=2)</i>	n(%)	n(%)	n(%)
Clinical diagnosis of acute ischaemic stroke causing measurable neurological deficit	58 (92)	89 (96)	180 (79)
Exclusion of Intracranial haemorrhage by appropriate imaging techniques ¹	59 (94)	90 (97)	NA
<i>Standard USA only (n=2)</i>			
Age > 18 years	57 (91)	81 (87)	179 (78)
Ability to start <3 hours from symptom onset	1 (1.6)	1 (1.1)	54 (24)
<i>Standard UK & AUS (n=1); Standard by USA Guidelines/Non-standard by USA Label</i>			
Ability to start <4.5 hours from symptom onset	62 (98)	92 (99)	172 (75)
<i>Non-standard all (n=4)</i>			
NIHSS > 4	31 (49)	47 (51)	80 (35)
Favourable CTP penumbra.	14 (22)	10 (11)	43 (19)
Occlusion on CTA	13 (21)	15 (16)	60 (26)
Age <80 years, for 3-4.5hr since onset	11 (18)	33 (36)	111(63) ² (65.7)
<i>Non-standard USA (n=1)</i>			
Order for IV rtPA given only by a neurologist	NA	NA	71 (31)
STANDARD EXCLUSION Criteria	AUS	UK	USA
Bleeding risk	n(%)	n(%)	n(%)
<i>Standard all (n=12)</i>			
Active Internal Bleeding	59 (94)	85 (91)	181 (79)
Clinical presentation suggestive of SAH, even if CT is normal	54 (86)	78 (83)	150 (66)
Known bleeding diathesis	51 (81)	75 (81)	160 (70)
INR >1.7	59 (94)	86 (93)	179 (78)
APTT greater than upper limit of normal on lab report	37 (59)	47 (51)	163 (71)
Prothrombin Time > 15 seconds	19 (30)	24 (26)	113 (49)
Platelet count of below 100,000/mm ⁴	47 (75)	53 (57)	170 (74)
History of serious head trauma or ischaemic stroke within 3 months of this event	52 (83)	78 (84)	180 (79)
History of structural lesions including arteriovenous malformation, aneurysms or tumours	49 (78)	71 (76)	161 (70)
History of intracranial haemorrhage at any point in the past	45 (71)	72 (77)	194 (85)

Past major surgery or serious trauma in past 3 months	43 (68)	64 (69)	174 (76)
Evidence of intracranial haemorrhage on CT-scan	50 (79)	83 (89)	NA ³
<i>Standard USA only (n=1)</i>			
Systolic BP > 185 mm Hg and/or diastolic BP > 110 mm Hg at the time of rtPA treatment	NA	NA	181 (79)
<i>Standard AUS & UK only (n=10)</i>			
Significant bleeding disorder at present or within last 6 months	40 (64)	69 (74)	NA
Recent arterial puncture at a non-compressible site	47 (75)	73 (79)	153 (67)
Neoplasm with increased risk of bleeding	35 (56)	60 (65)	NA
Manifest or recent severe or dangerous bleeding	40 (64)	73 (79)	NA
Severe uncontrolled arterial hypertension	40 (64)	60 (65)	NA
Systolic BP >185 or diastolic BP >110 mm Hg, or aggressive (IV) management	49 (78)	54 (58)	NA
History of gastrointestinal or urinary tract haemorrhage within 21 days	45 (71)	73 (79)	163 (71)
Recent (less than 10 days) traumatic CPR or obstetrical delivery	39 (62)	64 (69)	NA
Patients receiving other intravenous thrombolytic agents	31 (49)	58 (62)	NA
Any current use of anticoagulation regardless of coagulation study findings	14 (22)	15 (16)	51 (22)
Stroke severity and/or disability			
<i>Standard AUS & UK (n=4)</i>			
Symptoms beginning more than 4.5 hours / unknown onset time	48 (76)	72 (77)	NA
Severe neurological disability e.g. NIHSS >25	39 (62)	39 (42)	70 (31)
Prior stroke within the last 3 months	37 (59)	58 (62)	NA
Rapidly improving stroke symptoms, even if measurable disability remains	22 (35)	40 (43)	100 (44)
Comorbidity			
<i>Standard all (n=1)</i>			
Observed seizure at stroke onset	45 (71)	53 (57)	122 (53)
<i>Standard UK & AUS only(n=7)</i>			
Suspected post-myocardial infarction pericarditis	21 (33)	36 (39)	77 (34)
Acute pancreatitis	20 (32)	55 (59)	NA
Suspicion of endocarditis	32 (51)	47 (51)	58 (25)
Severe liver disease, including hepatic failure, cirrhosis, portal hypertension & active hepatitis	35 (56)	58 (62)	NA
Abnormal blood glucose; <50mg/dL (<2.8mmol/L) or >400mg/dL (22.2mmol/L)	53 (84)	53 (57)	133 (58)
Documented ulcerative gastrointestinal disease (last 3 months), oesophageal varices, arterial aneurysm, arterial/venous malformation	40 (64)	73 (79)	NA
Patients with any history of prior stroke and concomitant diabetes	9 (14)	19 (20.4)	NA

Demographics			
<i>Standard UK & AUS only(n=1)</i>			
Age <18 years	38 (60)	59 (63)	NA
NON-STANDARD EXCLUSION Criteria	AUS	UK	USA
Bleeding risk (n=5)	n (%)	n (%)	n (%)
Current use of novel anticoagulants (NOACS)	36 (57)	67 (72)	132 (58)
Use of continuous intravenous infusion to control blood pressure	18 (29)	22 (24)	17 (7.0)
Patients pre-treated with acetyl salicylic acid	1 (1.6)	7 (7.5)	NA
On other antiplatelet medication ⁴	NA	NA	12 (5.2)
Other conditions deemed high risk for haemorrhage ⁴	3 (4.8)	2 (2.2)	NA
Stroke severity and/or disability (n=4)			
Level of consciousness severely depressed (obtunded, stuporous or comatose)	39 (62)	39 (42)	16 (7.0)
Minor neurological disability	23 (37)	29 (31)	59 (26)
History of previous ischaemic stroke at any point in the past	5 (7.9)	7 (7.5)	NA
Large artery occlusion warranting primary intra-arterial treatment	1 (1.6)	8 (8.6)	31 (14)
Comorbidity (n=11)			
Pregnancy	47 (75)	38 (41)	112 (49)
Concurrent acute myocardial infarction	30 (48)	15 (16)	60 (26)
Serious, advanced or terminal illness ⁴	8 (13)	0	NA
Suspected septic emboli ⁴	8 (13)	0	NA
Elevated liver enzymes	4 (6.4)	17 (18)	NA
Not observed, but suspected seizure at stroke onset	18 (29)	21 (23)	45 (20)
Pre-existing moderate to severe disability (mRS >3/4) ⁴	7 (11)	9 (9.7)	NA
Known hypersensitivity to Alteplase or gentamicin ⁴	5 (7.9)	0	NA
Recent lumbar puncture	24 (38)	50 (54)	114 (50)
Myocardial infarction in last 3 months ⁴	1 (1.6)	0	NA
Lactation or parturition in last 30 days ⁴	1 (1.6)	0	NA
Demographics(n=4)			
Age >75 years	0	0	NA
Age > 80 years	8 (13)	3 (3.2)	36 (16)
Only to be used by physicians trained and experienced in the use of thrombolytic treat	11 (18)	40 (43)	NA
Inability to obtain written informed consent for on-label treatment	5 (7.9)	3 (3.2)	21 (9.2)

1 - This was specified as an exclusion on the USA survey and therefore not specified on inclusions. 2 – The 54 respondents that selected the standard USA criteria “Age <80 years, for 3-4.5hr since onset” were removed from the calculation. 3 - Haemorrhage on CT was specified as an exclusion on the USA survey, so these data were not collected. 4 - This was specified as an ‘other’ by respondents
NA = not applicable refers to a criterion that was not pre-specified in the country-specific survey.

SAH: Subarachnoid Haemorrhage; CT: Computed Tomography; CTP: Computed tomography perfusion; CTA: Computed tomography angiography; INR: International Normalised Ratio; APTT: Activated Partial Thromboplastin Time; BP: Blood Pressure; CPR: Cardiopulmonary Resuscitation; NIHSS: National Institute of Health’s Stroke Scale; mRS: Modified Rankin Scale; ROSIER: Recognition of Stroke in the Emergency Room Scale.

Supplement Table A Key stroke service demographics

Hospital setting	AUS (N=63)	UK (N=93)	USA (N=229)
	n (%)		
Tertiary	29 (46)	49 (53)	66 (29)
Non-tertiary	30 (48)	43 (46)	152 (66)
Private	4 (6.4)	0	0
Not Reported	0	1 (1)	11 (5)
Stroke service			
Comprehensive	24 (38)	Not Collected	157 (69)
Primary	31 (49)	Not Collected	64 (28)
General hospital	8 (13)	Not Collected	3 (1)
Not Reported	0	Not Collected	5 (2)
Level of telemedicine use			
Always	2 (3.2)	6 (6.5)	Not Collected
Often	8 (13)	17 (18)	Not Collected
Sometimes	9 (14)	33 (35.5)	Not Collected
Never	43 (68)	36 (39)	Not Collected
Unknown	1 (1.6)	0	Not Collected
Not Reported	0	1 (1)	Not Collected
rt-PA protocol			
Yes	62 (98)	92 (99)	NA*
No	1 (1.6)	0 (0.0)	NA*
Not Reported	0	1 (1)	NA*

*rt-PA protocols were required to participate in the survey.

Supplement Table B Associations between service related factors and rtPA treatment rates

	AUS			UK			USA		
	Mean (SD)	p-value	n	Mean (SD)	p-value	n	Mean (SD)	p-value	N
Hospital Setting¹									
Non-Tertiary	7.62 (5.22)	0.120	31	11.52 (4.77)	0.046	36	7.94 (5.72)	0.005	135
Tertiary	9.95 (6.22)		29	13.69 (4.52)		41	10.97 (7.68)		48
Average door to needle time²									
<45mins	15.68 (9.21)	0.131	3	14.88 (6.18)	0.067	20	16.51 (7.35)	<0.001	7
46-59mins	9.79 (6.21)		9	13.99 (4.00)		18	10.75 (7.68)		24
≥60mins	8.85 (5.09)		37	11.90 (3.14)		28	8.07 (5.89)		151

¹ Independent Sample t-test, ² One-way ANOVA

Supplement Table C

Factors associated with the addition of non-standard criteria

Variables entered in regression model	AUS N=49		UK N=68		USA N=184	
	Coefficients	p-value	Coefficients	p-value	Coefficients	p-value
Hospital Setting	-0.29 (-2.84, 2.25)	0.817	-0.83 (-2.39,0.72)	0.287	-1.72(-3.25, -0.20)	0.03
Service	0.06 (-2.35, 2.48)	0.958	NA		-0.28(-1.68, 1.10)	0.684
Admission volume	-0.00 (-0.01, 0.01)	0.983	-0.01(-0.04,0.00)	0.434	0.00 (-0.00, 0.00)	0.187
Average door to needle time (46mins to 59mins)	-1.33(-5.52, 2.86)	0.525	1.13(-0.86,3.12)	0.262	2.51(-1.05, 6.07)	0.165
Average door to needle time (>60mins)	0.60 (-3.34-4.54)	0.760	1.19(-0.67,3.05)	0.207	3.57 (0.38 ,6.75)	0.023
Adherence to 3 hours	NA		NA		-2.44(-4.30, -0.60)	0.01