**Time intervals and distances travelled for pre-hospital ambulance stroke care: data from the randomised-controlled ambulance-based Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial-2 (RIGHT-2)**

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## ABSTRACT

### Objectives

Ambulances offer the first opportunity to evaluate hyperacute stroke treatments. We investigated the conduct of a hyperacute stroke study in the ambulance-based setting with a particular focus on timings and logistics of trial delivery.

### Design

Multicentre prospective, single-blind, parallel group randomised controlled trial.

### Setting

Eight NHS ambulance services in England and Wales; 54 acute stroke centres.

### Participants

Paramedics enrolled 1,149 patients with likely stroke, face, arm speech (2 or 3), within four hours of symptom onset and systolic BP>120mmHg.

### Interventions

Paramedics administered randomly assigned active transdermal glyceryl trinitrate or sham.

### Primary and Secondary Outcomes

Modified Rankin scale at day-90. This paper focuses on response time intervals, distances travelled and baseline characteristics of patients, compared between ambulance services.

### Results

Paramedics enrolled 1,149 patients between September 2015 and May 2018. Final diagnosis: intracerebral haemorrhage 13%, ischaemic stroke 52%, TIA 9%, mimic 26%. Timings (minutes) were (median [25, 75 centile]): onset to emergency call 19 [5, 64]; onset to randomisation 71 [45, 116]; total time at scene 33 [26, 46]; depart scene to hospital 15 [10, 23]; randomisation to hospital 24 [16, 34] and onset to hospital 97 [71, 141]. Ambulances travelled (km) 10 [4, 19] from scene to hospital. Timings and distances differed between ambulance service, e.g. onset to randomisation (fastest 53, slowest 77 minutes; $p<0.001$), distance from scene to hospital (least 4, most 20 km; $p<0.001$).

**Conclusion**

We completed a large pre-hospital stroke trial involving a simple-to-administer intervention across multiple ambulance services. The time from onset to randomisation and modest distances travelled support the applicability of future large-scale paramedic-delivered ambulance-based stroke trials in urban and rural locations.

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Ambulance, paramedic, stroke, glyceryl trinitrate, logistics

## STRENGTHS AND LIMITATIONS

- The first multicentre paramedic-delivered ambulance-based randomised-controlled trial in stroke in the United Kingdom.
- Ambulance response time intervals and distances are collated and reported for 1,149 patients assessed as likely stroke.
- The time-interval between arrival at hospital and the ambulance becoming available for the next emergency call (hospital turnaround) is not captured, but worth considering for future trials
- Timing and logistic data may not be fully representative of all urban and rural locations due to non-participation of some hospitals and ambulance stations within ambulance service regional areas.

## INTRODUCTION

Routine pre-hospital management of suspected acute stroke involves rapid identification of suspected stroke using a validated stroke screening tool, prompt transport, pre-arrival notification and primary stabilisation to the nearest appropriate receiving stroke centre.[1] The mainstays for hyperacute management of stroke in hospital include urgent neuroimaging, stroke unit care, reperfusion therapy for ischaemic stroke, and blood pressure (BP) lowering for intracerebral haemorrhage.[2] For reperfusion therapies, shortening the time from symptom onset to treatment improves functional outcome and this has become the aim of pre-hospital and in-hospital acute stroke services.[3-6] Thus, ambulance services play a crucial role in assessing, identifying and conveying patients with suspected stroke to primary and comprehensive stroke centres, which may include bypassing local emergency departments.

Timely pre-hospital care for stroke is dependent upon several factors that include rapid recognition of potential stroke and calling for help,[7] ambulance response times encompassing symptom onset to arrival at hospital,[8] distance from scene to hospital,[9] and the accuracy of identifying patients with true stroke or transient ischaemic attack (TIA) from those with a stroke mimic.[10] There are a small, but growing number of studies that explore randomised paramedic-initiated interventions commencing in the ambulance for acute stroke. However, few studies have systematically analysed these parameters and the factors that influence them in acute pre-hospital stroke practice.[4 11-13]

Here, we report the logistics underlying patient recruitment to the Rapid Intervention with Glyceryl trinitrate (GTN) in Hypertensive stroke Trial-2 (RIGHT-2), a large ambulance-based stroke trial in the UK that investigated the efficacy of transdermal glyceryl trinitrate as a paramedic-delivered intervention in suspected acute stroke. Specifically, ambulance response times and distance travelled across multiple organisations in this setting are assessed.

## METHODS

### RIGHT-2 trial

RIGHT-2 (registration ISRCTN26986053) commenced recruitment in September 2015 with the first participant recruited on 22 October 2015.

RIGHT-2 was a multicentre prospective, single-blind, parallel group randomised controlled trial; the protocol, statistical analysis plan, baseline data, main results and subgroup results in participants with a final diagnosis of intracerebral haemorrhage (ICH) are published.[14-18] Briefly, adult patients with suspected stroke presenting to the emergency service via an emergency call were recruited if they: were FAST-positive (facial weakness, arm weakness, speech abnormality; with test score 2 or 3), had systolic BP of >120mmHg, were within 4 hours of symptom onset, presented to trial-trained paramedics from eight UK ambulance services, and were to be taken to a trial-participating hospital. Patients were randomised to receive transdermal glyceryl trinitrate (GTN) or sham patch in the ambulance and this was continued for three further days during hospital admission.[19] The study was undertaken across eight UK ambulance services (AS): East of England AS (EEAS), East Midlands AS (EMAS), London AS (LAS), South-Central AS (SCAS), South-West AS (SWAS), Welsh AS (WAS), West-Midlands AS (WMAS) and Yorkshire AS (YAS). All participating ambulance services used FAST identification and protocols consistent with national guidelines.

For each eligible patient, the enrolling paramedic assessed capacity and obtained patient or proxy consent (from a relative on the scene, or from the paramedic witnessed by a colleague), completed a written case report form to capture in-ambulance baseline and on-treatment data, and applied the transdermal patch of GTN or sham dressing.[14] Ambulance-related data not recorded at source were confirmed by research paramedics from participating ambulance services after review of control room timing logs or patient care records, and then entered into the trial database.

### Timings and distances

Timings were obtained from each ambulance service (time of emergency call, resource dispatch, scene arrival and departure, hospital arrival) and from paramedic records (consent for trial enrolment, randomisation, application of study treatment). Paramedic-documented history provided the time of symptom onset or, where unclear, the last known well time.

Distance measurements were calculated from the address or postcode of the emergency location, where available, to the expected stopping point for the ambulance at the destination hospital (accident and emergency or stroke unit entrance) to the nearest 10 metres using Google Maps; one ambulance service was unable to provide postcode information due to time constraints. One ambulance service was able to provide the linear distance from the location of the ambulance at the point of dispatch to the scene of the emergency.

A comparison of urban versus rural ambulance services arbitrarily divided ASs by <25% rural versus >25% rural (as defined in Table 1; Supplemental Table I).

**Table 1**. Characteristics of participating ambulance service as of 31st May 2018. Data are numbers (%)

| | E&W | EEAS | EMAS | LAS | SCAS | SWAS | WAS | WMAS | YAS |
|---|---|---|---|---|---|---|---|---|---|
| Time in trial (months) | 32 | 27 | 32 | 14 | 4 | 27 | 22 | 14 | 29 |
| Patients | 1149 | 178 | 218 | 202 | 7 | 265 | 89 | 37 | 153 |
| Participating hospitals | 54 | 5 | 10 | 3 | 1 | 13 | 4 | 5 | 13 |
| Area ($km^2$) | 122,065 | 19,424 | 16,710 | 1,605 | 9,204 | 25,899 | 20,735 | 12,949 | 15,539 |
| Population | | | | | | | | | |
| Overall (x1000) | 53,000 | 5,800 | 4,800 | 8,600 | 7,000 | 5,300 | 2,900 | 5,600 | 5,338 |
| Living in rural areas† (%) | 17.6 | 28.9 | 26.7 | 0.2 | 20.4 | 31.6 | 32.8 | 15.1 | 17.5 |
| Strokes (/yr) †† | 90,781 | 9,145 | 9,246 | 13,118 | 7,763 | 10,442 | 7,400 | 8,701 | 7,931 |
| Adjusted ratio /1000 | 1.71 | 1.58 | 1.92 | 1.52 | 1.11 | 1.97 | 2.55 | 1.55 | 1.49 |
| Call volume (/day) | 24,661 | 2,800 | 2,500 | 5,193 | 1,479 | 3,077 | 1,331 | 3,000 | 2,336 |
| Participating Ambulance Stations | 270 | 24 | 50 | 23 | 3 | 73 | 34 | 17 | 63 |
| Paramedics employed | 22,000 | 2,000 | 1,111 | 2,864 | 1,780 | 1,788 | 1,310 | 1,300 | 1,592 |
| Trained in RIGHT-2 | 1,492 | 145 | 193 | 325 | 63 | 313 | 165 | 124 | 142 |
| Paramedics who recruited | 516 | 58 | 75 | 120 | 6 | 112 | 47 | 23 | 75 |
| Patients/paramedic | 2.22 | 3.06 | 2.90 | 1.68 | 1.16 | 2.37 | 1.89 | 1.60 | 2.04 |

† 2011 Census[20] †† Number of suspected stroke patients assessed face-to-face 2015/6

E&W: England & Wales; EEAS – East of England Ambulance Service NHS Trust; EMAS – East Midlands Ambulance Service NHS Trust; LAS – London Ambulance Service; SCAS – South Central Ambulance Service NHS Foundation Trust; SWAS – South Western Ambulance Service NHS Foundation Trust; WAS – Welsh Ambulance Service NHS Trust; YAS – Yorkshire Ambulance Service NHS Trust.

**Comparison of trial and non-trial patients**

One ambulance service provided response time interval and distance data for a cohort (n=49) of confirmed stroke patients who were not enrolled into RIGHT-2 (attended by non-trial trained paramedics) but were transported to the same specialist stroke centres participating in the trial.

**Statistical Analysis**

Time intervals (in minutes), distances (kilometres, km) and baseline characteristics were compared between ambulance services using chi-square and Kruskal-Wallis (one-way ANOVA on ranks) tests. Multiple comparison procedures (Dunn's with Bonferroni correction) were used to assess which ambulance service differed from the others. Spearman and point-biserial correlations were performed to identify the relationship between baseline variables, times and distances. Data are number (%), median [interquartile range] or mean (standard deviation). Statistical significance was defined overall at $p<0.05$, and at $p<0.001$ for correlation matrices and multiple comparisons. Statistical analyses were conducted with SPSS version 24 (IBM, New York).

**Patient and Public Involvement**

This study was supported by public members of the trial steering committee who were involved throughout, including in trial design, development, conduct, periodic review and dissemination of results.

## RESULTS

RIGHT-2 recruited 1,149 patients between September 2015 and May 2018. Table 1 outlines patient recruitment across the various participating ambulance services, which collectively covered an area of 122,065 $km^2$ in England and Wales (i.e. 42% of the land area of these countries). Ambulance services varied considerably in size (1,605 $km^2$ vs 25,899 $km^2$), population served per service (2.9M vs 8.6M)[20] and annual stroke events (7,400 vs 13,118) (Table 1). Altogether 1,492 paramedics volunteered to be trained in the trial, of whom 516 (36%) recruited at least one patient. Where two or more trial paramedics were present at scene, the paramedic initiating randomisation was credited. On average, 2.2 patients were recruited by each paramedic who enrolled at least one patient although this varied between ambulance services (1.1 vs 3.1).

### Patient characteristics

Of the 1,149 patients recruited, average age was 73 (15) years, female 48%, BP 162 (25)/92 (18) mmHg, Glasgow coma scale (GCS) 13.9 (1.7), and FAST score of three 60% (Supplemental Table II). The final diagnosis varied between ambulance services, with the rate of conditions mimicking acute neurovascular disease ranging from 14.3% to 36.1%. This is consistent with other pre-hospital trials without physician presence or mobile stroke unit care, and the rate of stroke mimic reported here is explored elsewhere.[21] Baseline temperature also varied. Otherwise, baseline characteristics did not differ between ambulance service. As age increased, BP and glucose were higher, and heart rate, FAST and GCS lower (Supplemental Table III). 603 (53%) patients gave informed consent, 431 (38%) by relative and 115 (10%) by paramedic witnessed by a colleague on scene.

### Time Intervals

The time intervals for various stages in the journey from stroke scene to hospital are shown in Supplemental Table IV. Overall, the median time from symptom onset to emergency call was 19 [interquartile range 5, 64] minutes and this did not differ between ambulance services (Supplemental Tables IV and V). The median time from emergency call to ambulance dispatch was 3 [1, 7] minutes and varied between ambulance service (1 minute vs 5 minutes). An ambulance resource arrived at scene within 8 [5, 13] minutes from being dispatched (and 10 [6, 16] minutes if only including RIGHT-2 trained paramedics) with this varying between ambulance service

(8 minutes vs 12 minutes).

The median time from onset of symptoms to randomisation was 71 [45, 116] minutes (Table 2, Figure 1) and this varied between ambulance service (53 minutes vs 77 minutes). Significantly, randomisation occurred within 30 and 60 minutes of symptom onset in 104 (9.1%) and 491 (42.9%) participants respectively (Table 2). Ambulance resources spent a median of 33 [26, 46] minutes on scene, though this varied between ambulance services (29 minutes vs 43 minutes) (Supplemental Table IV). Importantly, time on scene did not differ significantly when comparing RIGHT-2 patients versus non-RIGHT-2 patients 34 [26, 44] and 32 [23, 41] minutes respectively (Supplemental Table VI). Transfer time from scene to hospital was a median of 15 [10, 23] minutes, but varied between ambulance service (9 minutes vs 24 minutes) (Supplemental Table IV). The overall time from symptom onset to arrival at hospital was 97 [71, 141] minutes and also varied between ambulance services (86 minutes vs 109 minutes) (Supplemental Table VII). Time at scene was strongly positively correlated with time from scene to hospital (Table 3).

**Table 2.** Timings: Symptom onset to randomisation (OTR) (minutes). Data are N (%), median [25, 75 centile]; comparison by Kruskal-Wallis test.

| **Minutes** | **E&W** | **EEAS** | **EMAS** | **LAS** | **SCAS** | **SWAS** | **WAS** | **WMAS** | **YAS** | **2p** |
|---|---|---|---|---|---|---|---|---|---|---|
| OTR | | | | | | | | | | |
| N (%) | 1149 | 178 (15.5) | 218 (19.0) | 202 (17.6) | 7 (0.6) | 265 (23.1) | 89 (7.7) | 37 (3.2) | 153 (13.3) | |
| Median [25, 75 centile] | 71 [45, 116] | 73 [47, 120] | 59 [35, 100] | 77 [51, 124] | 53 [45, 65] | 75 [49, 107] | 75 [48, 123] | 60 [32, 115] | 70 [45, 118] | 0.001 |
| N (%) | | | | | | | | | | <0.001 |
| ≤30 | 104 (9.1) | 15 (8.4) | 38 (17.4) | 11 (5.4) | 1 (14.3) | 16 (6.0) | 7 (7.9) | 6 (16.2) | 10 (6.5) | |
| 31-60 | 387 (33.8) | 63 (35.4) | 82 (37.6) | 61 (30.2) | 3 (42.9) | 82 (30.9) | 28 (31.5) | 13 (35.1) | 56 (36.6) | |
| 61-90 | 258 (22.5) | 32 (18.0) | 34 (15.6) | 51(25.2) | 0 (0.0) | 77 (29.1) | 19 (21.3) | 5 (13.5) | 38 (24.8) | |
| 91-120 | 136 (15.1) | 25 (14.0) | 19 (8.7) | 25 (12.4) | 0 (0.0) | 36 (13.6) | 13 (14.6) | 5 (13.5) | 13 (8.5) | |
| 121-180 | 173 (15.1) | 30 (16.9) | 33 (15.1) | 28 (13.9) | 0 (0.0) | 40 (15.1) | 16 (18.0) | 6 (16.2) | 20 (13.1) | |
| 181-240 | 76 (6.6) | 12 (6.7) | 9 (4.1) | 20 (9.9) | 0 (0.0) | 13 (4.9) | 5 (5.6) | 2 (5.4) | 15 (9.8) | |
| >240 | 15 (1.2) | 1 (0.5) | 3 (1.4) | 6 (3.0) | 1 (14.3) | 1 (0.4) | 1 (1.1) | 0 (0.0) | 2 (0.7) | |

**Table 3.** Univariate Correlation between severity of symptoms, timings and distance from scene to hospital. Data are Spearman's coefficient (p-value).

| | OTR | FAST | GCS | Scene | OTH | STH | Km |
|---|---|---|---|---|---|---|---|
| OTC | 0.836 (<0.001) | -0.130 (<0.001) | 0.086 (0.003) | 0.05 (0.088) | 0.802 (<0.001) | 0.007 (0.80) | -0.070 (0.033) |
| OTR | | -0.135 (<0.001) | 0.102 (0.001) | 0.263 (<0.001) | 0.941 (<0.001) | 0.244 (<0.001) | -0.61 (0.61) |
| FAST | | | -0.157 (<0.001) | -0.066 (0.026) | -0.133 (<0.001) | -0.046 (0.12) | 0.803 (0.93) |
| GCS | | | | -0.008 (0.80) | 0.115 (<0.001) | 0.084 (0.004) | 0.076 (0.017) |
| Scene | | | | | 0.326 (<0.001) | 0.791 (<0.001) | 0.104 (0.002) |
| OTH | | | | | | 0.403 (<0.001) | 0.216 (<0.001) |
| STH | | | | | | | 0.554 (<0.001) |

OTC: onset to emergency call; OTR: onset to randomisation; FAST: face, arm, speech, time score. Scene: Total time spent at scene; STH: Time from scene to reach hospital; Km: distance (kilometres) from scene to hospital.

## Distances

The median distance travelled from the postcode of the suspected stroke scene to the receiving hospital was 10.0 [4.4, 18.4] km, with considerable variation between ambulance services (4.1 km vs 19.9 km) (Supplemental Table VIII). Time from scene to hospital was moderately positively correlated with distance from scene to hospital. (Supplemental Figures I:A-G present geographical distribution of randomisation by ambulance service)

## Urban versus rural services

When comparing urban and rural ambulance services (Supplemental Table I), there was no difference in receipt of the emergency call to dispatching a resource to scene, nor a difference in onset of symptoms to randomisation. The time spent at scene was marginally longer in rural locations and, as anticipated, both conveyance time and distance to the stroke centre was statistically different.

## Comparison of trial and non-trial patients

In the ambulance service with times available for patients not enrolled in the trial, on scene to hospital arrival differed among patients enrolled and not enrolled in RIGHT-2, 10 [0.4, 64.7] versus 16 [7.6, 24.0] minutes (Supplemental Table VIII). The median distance from dispatch location to scene in the ambulance service with this available (EMAS) was 7.3 km [3.5, 12.0].

## DISCUSSION

In this large national prehospital trial, 516 paramedics from eight ambulance services across England and Wales successfully recruited 1,149 participants and transported them to 54 hospitals. Paramedics assessed and diagnosed suspected stroke, consented patients and initiated randomised treatment. Key timings were: onset to emergency call 19 minutes, onset to scene 40 minutes, onset to randomisation 71 minutes, time at scene 33 minutes, randomisation to hospital 24 minutes, and depart scene to hospital arrival 15 minutes; all but the first two differed between ambulance services. The average distance travelled by one ambulance service from dispatch location to scene was 7.3 km and 10.0 km from scene to hospital for all participating ambulance services.

Pre-hospital time intervals in acute stroke have been described previously,[12 22-26] but rarely in randomised trials.[4 11 13] The symptom onset to randomisation time of 71 minutes in RIGHT-2 is consistent with two previous UK ambulance-based stroke trials (RIGHT 55 minutes; Paramedic Initiated Lisinopril For Acute Stroke Treatment (PIL-FAST) 70 minutes)[27 28] although these were small single centre pilot studies undertaken largely in urban settings. The large US Field Administration of Stroke Therapy - Magnesium trial[29] (FAST-MAG) reported a median of 45 minutes from symptom onset to receipt of study drug. Nevertheless, these times are all longer than UK multi-centre ambulance-based trials outside of stroke, notably the AIRWAYS-2 and PARAMEDIC-2 trials in cardiac arrest.[30 31] In PARAMEDIC-2, the onset of symptoms to initiation of treatment in the intervention group was just 21.5 minutes. The most important driver of this difference is most likely shorter onset to call times for cardiac arrest patients than for stroke, and suspected stroke may require more complex assessment both by call handlers and by paramedics on scene. Additional contributors are that cardiac arrest is allocated the highest dispatch priority, an immediate response and patients receive immediate trial treatment with emergency waiver of consent.

The explanation for differences in timings is probably multifactorial but the degree of urban versus rural population is one likely explanation. This was apparent for time spent at scene and both time and distance to hospital. As expected, there were no differences for receipt of call to dispatch, arrival of RIGHT-2 trained paramedic at scene nor onset of symptoms to randomisation.

There are several strengths of this study. First, RIGHT-2 involved eight of 11 ambulance services in England and Wales. Of those not participating, two were unable to join because they were involved in another ambulance-based stroke trial[32] and the other involved hospitals that were concerned about adversely impacting on recruitment to commercial trials. 516 paramedics (of 1,492 trained in RIGHT-2 procedures) consented and randomised a large number of participants, adhered to the protocol and completed specific data recording. It is noted that there are marked differences in recruit numbers between ambulance services. This, in part, is accounted for due to low recruitment during the initial recruitment phase requiring broadening of ambulance services from five to eight and stroke centres from 30-54. Furthermore, recruitment hours initially limited to typical working hours for research staff availability were extended to encompass 24/7 recruitment reflective of real-world ambulance care to not limit participation and maximise inclusion. Conflictingly, a small number of stroke centres closed recruitment to ambulances once target numbers of participants had been received and before the end of the recruitment phase highlighting the challenging reliance on dual centres when dealing with research in pre-hospital stroke.

Second, the consent model applied in RIGHT-2 is unlike any other large-scale ambulance-based studies worldwide to date and builds upon previous UK based pre-hospital stroke pilots.[27 33] Other pre-hospital trials in stroke have relied upon models of either informed consent,[34] deferred consent[35] or consent by doctor (present or remote).[29 36] Stroke is complex due to the varying nature of severity of presentations where patients' ability to consent in an informed manner to participate in a clinical study should not be overlooked preserving patient autonomy in accordance with the declaration of Helsinki.[37 38] Notwithstanding the complexities of emergency presentations that could impact upon decision-making, mental capacity or short intervention windows and the impact these situations bring to truly informed patient consent, the combined consent approach in RIGHT-2 acknowledges patient autonomy without precluding participation from those who are unable to voice their opinion or who lack presence of a proxy to consent on their behalf.[38] Mechanisms to safeguard consent were built into the protocol through reconfirmation of consent once in hospital for the both the pre-hospital and in-hospital elements respectively, and patient and public representatives were fully embedded within protocol development and steering group oversight of the trial.[14]

Third, the protocol required flexibility and adaptation to align with individual operational processes specific to each ambulance service to ensure successful delivery of the trial. Fourth, detailed logistic information on timing and distances travelled were collected. Last, the results highlight the successful delivery of a simple, ambulance-based intervention with 43% of patients receiving the intervention within two-hours of symptom onset without compromising time on scene required to complete additional research activity.

There are also several study limitations. Firstly, it is recognised that not every receiving stroke unit within each ambulance service region could participate in RIGHT-2 due to capacity and competing research,[32 39] (this included concurrent commercial and post-arrival trials). Therefore, it must be considered that the timing and logistic data of participating hospitals may not be fully representative of all urban and rural locations. However, the intention was not to assess the differences between urban and rural settings, but to shed light on the conduct and deliverability of a pre-hospital intervention in stroke where time and distance may impede access to specialist stroke services. Furthermore, stroke unit hours of operation varied across the 54 centres with a small number of sites not accepting patients outside working hours which impacted paramedics' decisions to randomise. This reduces the reflection of real-world emergency stroke care. The duration of recruitment varied between regions due to complexities in setting up multi-centre research

Additionally, it is acknowledged that the recruitment criteria were broad which resulted in a higher than anticipated proportion of stroke mimics. To mitigate this, mobile stroke unit care is an emerging field where imaging and definitive care delivery at the scene reduces time delays in stroke[40] and could offer improved confidence and precision of diagnosis for prehospital trial enrolment.

Recognising that 516 of 1,492 RIGHT-2 trained paramedics (36%) identified and randomised eligible patients, this is consistent with other trials in pre-hospital stroke.[27] This, in part, is due to the voluntary participation of paramedics in research where records suggest that only one third of the paramedic workforce participate.[41] Further, in a UK system where response time is one benchmark of the quality of ambulance service provision, ambulance dispatchers are not able to assign specific research-trained personnel to specific emergency calls, instead allocating the nearest available resource to attend. Low recruitment must be considered during the development of ambulance-based trials and this factor alone has previously resulted in extended recruitment phases, retraining of researchers and extensive study drug availability to achieve pre-planned sample sizes.[29 35 42]

Finally, this paper does not capture the time-interval between arrival at hospital and handover to the hospital team, nor the time of the ambulance becoming available for the next emergency call (hospital turnaround). During the hospital turnaround period, ambulance staff hand-over the patient to hospital staff, complete relevant documentation and prepare the vehicle for the next assignment. A rapid hospital turnaround is important for making the vehicle available for waiting emergency calls. Whilst the addition of research activity at scene may not delay enrolled patient treatment, it is possible that delay required to complete additional research activity steps after patient handover may prolong the turnaround phase.

In summary, we completed a large pre-hospital stroke trial involving a simple-to-administer intervention across multiple ambulance services. The time from onset to randomisation and modest distances travelled support the applicability of future large-scale paramedic-delivered ambulance-based stroke trials in urban and rural locations. Nevertheless, pre-hospital time intervals and distances from scene-to-hospital varied by ambulance service and this was, at least in part, explained by the type of urban versus rural population. Although our results may not be generalisable to all ambulance service settings, they do inform future developments in ambulance-based stroke care and provide support to the deliverability of future large-scale multicentre pre-hospital paramedic-delivered ambulance-based acute stroke trials.

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**ETHICAL APPROVAL**

RIGHT-2 was approved by the UK regulator (Medicines and Healthcare products Regulatory Agency, reference: 03057/0064/001–0001; Eudract 2015–000115–40) and national research ethics committee (IRAS: 167115) and was adopted by the National Institute for Health Research Clinical Research Network.

**TRANSPARENCY**

The lead and senior authors affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

**DATA AVAILABILITY STATEMENT**

Individual participant data are shared with the Blood pressure in Acute Stroke Collaboration (BASC) and Virtual International Stroke Trials Archive (VISTA). No further data available.

**CONTRIBUTORSHIP STATEMENT**

PMB, also principal investigator, and MD conceived the study. All authors contributed to the planning, design and conduct. LJH was responsible for data curation. PS and LJW supported with statistical analysis. All authors contributed to the reporting, analysis and interpretation of the results. MD and PMB led the writing of the manuscript with critical revision from JPA, PS, LJW, LJH, DH, JW and ANS.

**COMPETING INTERESTS**

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**Figure 1. Box Plot of Onset to Randomisation**

*See separate file*