Views of Paramedics on Their Role in an Out-of-Hospital Ambulance-Based Trial in Ultra-Acute Stroke: Qualitative Data From the Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT)

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Study objective: Optimal practices for recruiting, consenting, and randomizing patients, and delivering treatment in out-of-hospital ultra-acute stroke trials, remain unclear. We aim to identify key barriers and facilitators relevant to the design and conduct of ambulance-based stroke trials and to formulate preliminary recommendations for the design of future trials.

Methods: Using semistructured interviews, we investigated the experiences and challenges faced by paramedics who took part in a randomized controlled trial in suspected ultra-acute stroke, the Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT), in which recruitment, consent, randomization, assessment, and treatment were delivered by paramedics before hospitalization.

Results: We purposively selected a diversity sample of 14 of the 78 paramedics who participated in RIGHT. We identified 13 themes (7 facilitators and 6 barriers to out-of-hospital stroke research). A simple stroke diagnostic tool, use of proxy consent on behalf of patients, and straightforward trial processes were identified as the main facilitators. Recruitment became easier with each new randomization attempt. Key barriers reported were informed consent in the emergency setting, lack of institutional support for research, learning curve and rarity (each paramedic treats only a few eligible patients), and difficulty in attending training sessions. Interviewed paramedics were motivated to participate in research.

Conclusion: Ultra-acute stroke research in the out-of-hospital environment is feasible, but important barriers need to be addressed. Proxy consent by paramedics addresses some of the difficulties with the consent process in the out-of-hospital setting. [Ann Emerg Med. 2014;■:1-9.]

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INTRODUCTION

Background

Out-of-hospital treatment is standard in medical emergencies such as acute myocardial infarction and asthma, and can reduce time to treatment. Stroke treatments are also highly time dependent.[1] In ultra-acute stroke, there have been several approaches to reduce time to treatment, such as ambulances specifically equipped with computed tomography scanner and point-of-care laboratories, and with medical and nursing staff delivering treatment at the emergency site.[2,3] However, some interventions to manage neuroprotection and physiologic disturbances (eg, high blood pressure, hyperglycemia, pyrexia) do not need previous imaging and can be delivered by paramedics before hospitalization, without the need for new staff or equipment.

Importance

The lack of research in ultra-acute out-of-hospital stroke settings is a key concern and out-of-hospital treatment of stroke is a recognized research priority.[4,5] In a pilot study, the Rapid Intervention With Glyceryl Trinitrate in Hypertensive Stroke Trial (RIGHT), we showed that paramedics can successfully deliver treatment (transdermal glyceryl trinitrate) in a randomized clinical trial setting within an existing ambulance service infrastructure, thereby reducing treatment time.[6] Out-of-hospital ambulance-based paramedic-delivered trials have the potential to identify treatments that could improve clinical outcomes,[6,7] but larger studies are now needed to assess clinical efficacy.[8]

Qualitative investigations in the feasibility phase of a trial can inform the design of subsequent research[9] to maximize its

Editor's Capsule Summary

What is already known on this topic

Out-of-hospital research depends on the commitment and skill of emergency medical services providers, but they are often not a part of the planning process.

What question this study addressed

This qualitative study of select paramedics involved in a stroke trial used semistructured interviews to identify barriers and successful approaches in out-of-hospital research.

What this study adds to our knowledge

Paramedics identified difficulties with the informed consent process as the greatest obstacle to enrollment and stressed the importance of streamlining all steps in the research process that are conducted in the field.

How this is relevant to clinical practice

Knowledge of paramedics' experiences can help improve the out-of-hospital research process.

likelihood of success. One form of qualitative investigation involves seeking participants' views and experiences. For out-of-hospital ambulance-based stroke research, the key participants are paramedics. We gathered their reports of experiences and challenges faced in recruiting or attempting to recruit to an out-of-hospital stroke trial.

Goals of This Investigation

In this qualitative interview study, we gathered and examined paramedics' reports of the experiences and challenges they faced in recruiting or attempting to recruit patients to RIGHT.[6] The aim was to identify key barriers and facilitators relevant to the design and conduct of this ambulance-based stroke trial and to formulate preliminary recommendations for the design of future trials.

MATERIALS AND METHODS

Setting

RIGHT was jointly conducted by the University of Nottingham, East Midlands Ambulance Service National Health Service Trust, and Nottingham University Hospitals National Health Service Trust. The trial was run in accordance with the Declaration of Helsinki (1996) and Good Clinical Practice (GCP), and had approvals from the Medicines and Health Regulatory Authority (EudraCT number 2007-004766-40, January 21, 2009), local research ethics committee (reference 09/H0408/5, April 8, 2009), Nottingham University Hospitals National Health Service Trust (Research & Development Department, September 30, 2009), and East Midlands Ambulance Service National Health Service Trust (Research & Development Department, September 18, 2009).[6,10]

The study assessed the feasibility of paramedics performing all aspects of a clinical trial, namely, screening, consent, randomization, treatment, and measurement. The trial protocol and the quantitative outcomes have been published previously.[6,10] Adult patients with suspected stroke (facial drooping, arm weakness, speech difficulties, and time [FAST] test score of 2 or 3)[11] and hypertension, within 4 hours of stroke onset, presenting to research-trained paramedics were randomized to glyceryl trinitrate (a nitric oxide donor) or no glyceryl trinitrate. Glyceryl trinitrate was chosen because it decreases blood pressure,[12-14] an easily measured physiologic parameter in the ambulance environment, and because high blood pressure is both common and associated with a poor outcome after stroke.[15-17]

In the context of a 999 call for suspected stroke, and assessment of study eligibility, potential patients were approached by the paramedic to take part in the study. They explained the trial to the patients, guided by a single-page information sheet. If the patients understood the trial details and agreed to take part in the study, they were asked to sign a consent form. For patients lacking capacity, their relatives, if present, were approached to provide proxy consent. When a patient was unable to provide consent and no relative was present, research paramedics gave proxy consent on behalf of patients. Once the patient arrived at the hospital, the hospital researcher discussed the trial and obtained a detailed written informed consent from the patient or relative within 24 hours of hospital admission.

Study Design

We designed and conducted a qualitative substudy nested within the main trial. Semistructured, face-to-face interviews, using an interview aide-mémoire (Figure 1), were conducted by one of the trial researchers (S.A.), with wording and communication during actual interviews fitted to the individual conversations and interviewees. A mutually convenient time and place were arranged, and interviews were conducted either in the participant's ambulance station or the stroke research office at the University of Nottingham. The questions covered 6 key areas: stroke research, stroke diagnosis, consent, trial processes, recruitment, and training. The interviewer also explored other relevant issues that participants raised. Additional information collected included demographic information about the paramedic, ambulance station, length of service, and current role. Each interview lasted approximately 40 minutes and was recorded with a digital audiorecorder. Sample size was determined by both feasibility and thematic saturation.[18]

Selection of Participants

Seventy-eight paramedics participated in the RIGHT trial (Figure 2), of whom 23 recruited 1 or more patients. The

Introductory Question

Tell me something about yourself. Why are you taking part in the RIGHT trial?

Main Questions

(Starting questions are in italics and follow-up questions and probes are in bullet points.)

Can you recount for me the first time you attempted to randomize a patient into the trial?

- *Diagnosis*
- *Uncertainty*
- *Operational issues, eg, delay*
- *Consent issues: relatives, patients*
- *Paramedic's concerns*

For paramedics who attempted to randomize on more than 1 occasion, follow the same line of questioning with regard to their second attempt, including asking about any differences between the 2 occasions.

For those who attempted randomization several times, ask the following questions:

What's been the best or easiest part of the recruitment process?

What's been the most difficult part of the recruitment process?

Ask all participants:

Are there things about the way that the trial was set up that need improving to help people like you take part in it?

- Method to distribute IMP to ambulance stations and paramedics

Written and verbal communication between paramedics and research staff

We are hoping to repeat this kind of trial. In an ideal world, what should be different about the design of it the next time around?

Final Question

Are there some other issues that you had thought of that we haven't talked about yet?

Figure 1. Interview aide-mémoire. *IMP*, Investigational medicinal product.

7 paramedics who recruited 2 or more patients accounted for 25 (61%) of the 41 patients recruited to RIGHT.

All paramedics who had been trained for the main trial were eligible for the qualitative substudy. Information about the substudy was provided at investigator meetings and in trial newsletters. Participants were selected purposively from eligible paramedics to ensure diversity of paramedic experience and ambulance stations from where they operated, experience with screening but not recruiting patients, and experience with actually recruiting patients.

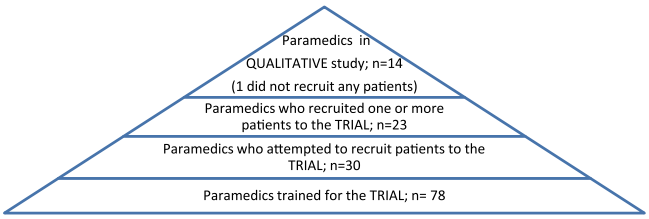

Figure 2. Paramedic participation in the RIGHT trial and nested qualitative study.

Of the 14 paramedics interviewed, 3 had screened 4 or more patients, 6 had recruited more than 1 patient, 7 had recruited 1 patient, 1 had not recruited any patients, 4 were paramedic team leaders, 3 were working in first response vehicles, 3 were working in ambulance stations more than 12 miles away from the admitting hospital, and 3 worked in stations that were less than 5 miles from the admitting hospital. Participants were provided with a written and verbal explanation of the study. Each participant signed a consent form.

Data Collection and Processing and Primary Data Analysis

The digital audiorecorded interviews were transferred to a password-protected folder on the investigator's work desktop computer. Interviews were transcribed verbatim and anonymized, using pseudonyms for personal names. The anonymized transcripts of the recorded interviews formed the data for analysis. Data analysis was carried out concurrently with data collection. Interview data were treated as reporting actual experiences and perceptions of the interview participants; that is, we took a realist perspective to analysis. Systematic, thematic content analysis, as described by Braun and Clarke,[19] was performed (Figure 3). S.A. conducted the initial reading, coding, and preliminary categorization of all transcripts. R.P. and A.N.S. then reviewed sections of the transcripts, selected by S.A., and revised the coding and categorization. After thematic categorization, the transcripts were circulated to all authors, who again read relevant parts to confirm accuracy and categorization. Themes were then classified as facilitators or barriers to of out-of-hospital stroke research, and in a final stage, we formulated preliminary recommendations for future trial design based on synthesis of the findings within the themes.

RESULTS

Fourteen of the 19 paramedics we approached participated in the interview study; the remaining 5 agreed but were unable to attend interviews because of intervening work commitments. Their length of experience as a paramedic ranged from 2 to

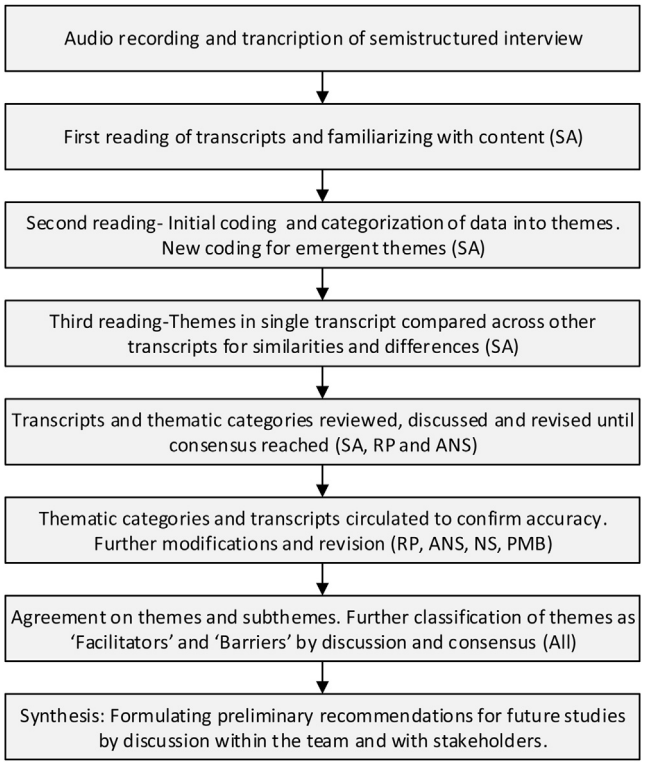

Figure 3. Data analysis process.

34 years. In Figure 4, we summarize the facilitator and barrier themes in relation to out-of-hospital stroke research We then flesh out these themes and illustrate with quotes from paramedics. Because 1 paramedic did not recruit any patients in the study, his views contributed little to the facilitator themes but did contribute to the barrier themes.

Facilitators of Out-of-Hospital Stroke Research

Paramedics' Motivation to Participate in Stroke Research (F1). The paramedics reported they wanted to be involved in stroke research to make a difference to their patients. They believed that patients with stroke had been neglected in the past and wanted to play a part in improving stroke care. Some had personal experience of stroke occurring in their loved ones, and this motivated them to take part in the research. The paramedics also thought participating in research helped them to network with other professionals and helped in career building:

> *I certainly have cared for stroke patients even at the beginning of my paramedic and ambulance work when strokes were very much you just grabbed them and manhandled them onto an ambulance and drove them and sat them in an A&E department waiting for their rehabilitation to start. Just compared with how we dealt with heart attacks I could just see you know this void between, and it just seemed very wrong. "Sorry about that; let's get you into some physiotherapy." So a trial that was looking at reducing the long-term effects and the effects that these sort of things are on people's lives are it's huge isn't it, not just for them but family and health service costs and all those sorts of things, so I was really pleased to be involved in a trial that was looking at to reduce that because it did seem to me that not a lot prior to that was done. (Paramedic 9)*

Facilitators of out-of-hospital stroke research

1. Paramedic's motivation to participate in stroke research
   a. Perception that this could make a difference to patient care
   b. Networking and career building
   c. Personal experiences of stroke affecting loved ones
2. Stroke diagnosis is straightforward
   a. Familiarity with FAST test
   b. Low skill set needed to learn the FAST test
3. Facility for paramedics to provide proxy consent
4. Stable and improving patients who are able to participate in consent conversations
5. Straightforward trial processes
6. Experience: Paramedics became more confident after first randomization
7. Positive experience of training and trial updates

Barriers to out-of-hospital stroke research

1. Lack of institutional support for research time
2. Absence of standardized performance of the FAST test
3. Informed consent process in the emergency out-of-hospital setting
   a. Time constraints
   b. Challenges associated with diagnostic disclosure and emotional sequelae of acute stroke
   c. Information needs of the patient or relative and of non-trial paramedics
4. Difficulty in maintaining IMP log
   a. Movement of ambulance vehicles between ambulance stations in the region
5. Factors leading to low proportion of eligible stroke patient recruitment
   a. Lack of continuous hospital stroke research cover
   b. Learning Curve (first recruitment perceived as particularly challenging)
   c. Rarity (individual paramedics treat only a few stroke patients each month)
   d. Not all paramedics in region are part of the clinical trial
6. Difficulty in organizing face-to-face training sessions
   a. Shift-work pattern
   b. Lack of institutional infrastructure for research

Figure 4. Facilitators and barriers to out-of-hospital stroke research.

Stroke Diagnosis is Straightforward (F2). In the whole RIGHT cohort, the diagnosis of stroke or transient ischemic attack made by the paramedic was confirmed by the admitting team in 36 of 41 patients (88%).[6] The paramedics stated they were confident in categorizing their patients as having probable stroke and were comfortable using FAST,[11] which was easy to remember and perform in the field. This also meant that the trial requirements were not different from what was already performed by the paramedics as routine evaluation:

> *It's quite easy, really, is we tend to obviously you do your face, arms, speech, and I usually do the legs if it is not that obvious; then you do and little things like that, but it is so easy to remember, easy to do, and it's what we do anyway. (Paramedic 13)*

Stable and Improving Patients Able to Participate in Consent Conversations (F3). The paramedics acknowledged that they were not used to taking explicit consent routinely from patients but understood its importance in research. Consent was relatively straightforward in some cases. The degree to which it was straightforward depended on the clinical stability of the patient and the mental composure of the patient or relative(s). The interview accounts suggested that the process of consent was made easier when the paramedic felt knowledgeable about the trial, was able to explain the study in simple terms, was able to show a caring and confident attitude, and had made a previously successful recruitment attempt.

Facility for Paramedics to Provide Proxy Consent (F4). For 11 of 41 (26.8%) of the recruited patients, the paramedics provided proxy consent for those who were unable to provide consent and when no relative was present.[6] All of the 11 patients or their relatives subsequently provided continuing consent to participate in the hospital phase of the trial. Paramedics reported that they were happy to provide such consent and did not express concerns about the process. The facility to provide proxy consent enabled recruitment of patients who would not have otherwise been included.

Straightforward Trial Processes (F5). The paramedics reported that the RIGHT trial processes were relatively simple and straightforward. They noted aspects of the trial that made it easier to recruit patients, including limited inclusion and exclusion criteria, brevity of the information sheet for patients and relatives that was provided in the trial pack, an investigational medicinal product that was simple to use, a limited amount of paperwork and data collection, and inclusion of an aide-mémoire (trial processes and consent) within the trial paperwork. The paramedics noted that although other methods of investigational medicinal product administration (intravenous, intramuscular, etc) might make future trials more complicated, they were trained and well equipped to carry out such procedures.

> *We need something that is easy to follow because anything that is lengthy or complicated will be rightly or wrongly dismissed as tricky, hard for the paramedics to do. You know it's got to be easy. (Paramedic 5)*

Experience: Recruitment Becomes Easier Following First Randomization (F6). As noted above, 25 (61%) of the 41 patients recruited to the RIGHT study were randomized by 7 of 78 (9%) of the paramedics who had been trained in preparation for RIGHT.[6] That is, less than 10% of paramedics trained recruited the majority of the patients. These paramedics reported that recruitment was easier after the first attempt at randomization as they became more familiar with trial processes:

> *I know what to look for. I know what piece of paper I want out of the envelope. I know what to be asking the patient. I know what to be looking for and that I can be doing 2 or 3 things at the same time as doing the observations. I can be cannulating and I can be talking to a patient and a relative and explaining what is happening to them all in the same go. (Paramedic 3)*

Positive Experience of Training and Trial Updates (F7). The paramedics thought that the in-house training sessions provided the necessary information about the trial background and procedures. They said they valued being kept updated about ongoing patient recruitment by e-mail and enjoyed reading the trial newsletters. They believed that regular and continued paramedic training was essential because each individual treated only a few patients with stroke each month. Involvement of paramedic clinical team leaders (responsible for the management and development of an ambulance station team) and research champions (paramedics funded to support the trial) was also seen as helpful, particularly in facilitating provision of training sessions in each ambulance station. Paramedic team leaders who took part in the study were keen to be involved in training and thought that the sessions were more successful in recruiting paramedics than would be mere written invitations to participate. Because of logistic difficulties in organizing face-to-face meetings and training, paramedics believed that for future trials, additional training resources such as DVDs or Web-based training could help with the training process.

Barriers to Out-of-Hospital Stroke Research

Lack of Institutional Support for Research Time (B1). The paramedics did not have dedicated research time allocated within their workload or contracts, though they reported they wanted it. They had to undertake research-related training in their personal unpaid time, which may have discouraged some paramedics from taking part in research:

> *I think that we should be proactive and that [East Midlands Ambulance Service] should be making itself one of the leading ambulances services in the country and we should be really proactive and be encouraging all staff to get involved, and pay staff the time to get involved or give them the time back to get involved; it disappoints me from that point of view. (Paramedic 3)*

Absence of a Standardized Way of Performing FAST (B2). The paramedics received training at work to conduct FAST assessment for suspected stroke patients, but some interview reports indicated variation in how the test was performed in the

field. One thought that better standardization of practice could help in achieving consistency for clinical trial purposes:

I would just look get some sort of grin, possible frowns, raised eyebrows. But again some people would just look for the droop, some people would just get a smile or whatever, some people would only try it once, some people would have a go again; you know what I mean. For arm weakness, put 2 fingers in and grip, but some people will pull and push and lift and hold your arms up; there are different ways people can do it. (Paramedic 9)

Informed Consent in the Emergency Out-of-Hospital Setting (B3). *Time Constraints of an Acute Medical Emergency* Consent was challenging for some paramedics, particularly on occasions in which there were conflicting priorities; for instance, between the needs of trial recruitment and consent procedures and patients' and relatives' needs for managing other concerns before admission. The paramedics had conflicting demands on their time in terms of ensuring that patients received optimum medical care within a limited period while explaining the trial to seek informed consent. There were also conflicting demands with regard to supporting relatives while explaining and implementing the trial. The paramedics expressed concerns that patients and relatives may not have been able to absorb all the information provided in the short time frame, and one paramedic was concerned that on one occasion, a patient's relative may have felt pressured to include her husband in the study:

And the family are worrying about is heating turned off, is the cat going to be fed. You know what I mean. It is not just around the care of the patient. They are trying to sort their whole life in 10 minutes as you are trying to get them onto an ambulance. (Paramedic 9)

A further demand on time on some occasions was the need to explain the trial to accompanying paramedic crew who had not received training and information on the study. Overall, this meant the exchange of information felt difficult and rushed on some occasions:

I mean, this is where it can get a little bit tricky in trials as well because sometimes they will want to know quite a bit, and for us, we are in the back of an ambulance. There may just be 2 of us, and the other individual is a driver, so you are on your own. You have to look after your patient. You have got to be keeping an eye on observations, but then potentially you have got quite a few questions to answer as well. (Paramedic 10)

We had lost a bit of time on the scene from getting him in the ambulance and…[were] always aware of time frame… and also getting the consent and then trying to explain it but not rush it through. It's very difficult and it is obviously distressing for the patient and the relative as to what is happening to them. (Paramedic 3)

Challenges Associated with Diagnostic Disclosure and Emotional Sequelae of Acute Stroke As evident in the foregoing quote from Paramedic 3, the occurrence of stroke is a stressful event and can be overwhelming to patients and their relatives. Paramedics thought that there was a risk of upsetting patients or relatives at the point when they were prompted by trial procedures to mention the diagnosis; disclosure of diagnosis is more traditionally made by the hospital clinical team. It was sometimes also difficult to inform the patient and relatives about both the diagnosis and the trial within the same episode:

His wife was being transported with him, so obviously she was a bit emotional, a bit emotive and stuff. It was quite a young guy from what I can remember. You know he did not have that massively grown-up children. (Paramedic 11)

What I find difficult is telling the patient what's happening, that initial "so and so believe they are having a stroke"; that's going to upset them definitely. They tend to. I think patients get a shock because they expect to hear that from doctors, so…when a paramedic starts saying that this is happening and this is happening, it is quite a shock to them. And it does—in my experience, it does tend to upset people. (Paramedic 10)

I think it is…more emotionally charged—the RIGHT trial—as obviously if there is family on scene they can be very emotional because their loved ones are having a stroke, and so it is upsetting for the individual and for the family. (Paramedic 10)

Difficulty in Maintaining the IMP Log (B4). In the RIGHT trial, the investigational medicinal product was initially packed in a brown folder along with the trial paperwork.[10] Although a log was maintained at each ambulance station, some envelopes were left in the ambulances and subsequently misplaced or lost when vehicles were moved for servicing or transferred to another ambulance station. Subsequently, the investigational medicinal product was dispatched in blue plastic folders to make it more obvious. One participant thought that some paramedics did not recognize the importance of maintaining an accurate log of the investigational medicinal product:

I think ultimately the ambulance service is such a widespread organization we are going to lose things, but I think that people did not appreciate that effectively a research product that you use like the envelopes pretty much has the same audit characteristics as…a controlled drug. Everyone knows the significance of having 1 morphine missing and the problems that that can cause. (Paramedic 11)

Factors Leading to Low Proportion of Eligible Stroke Patient Recruitment (B5). As noted, 41 patients were recruited to RIGHT during 20 months. Nineteen of these patients were randomized outside working hours (8:30 AM to 6 PM). However, after only 4 months of screening patients admitted to the Nottingham City Hospital Stroke Unit, we could identify a further 41 patients who satisfied the eligibility criteria but were not recruited into the study.[6] This suggests that many eligible patients may not have been approached for the study. Reasons for this arising within the interviews included paramedics' relative unfamiliarity with acute stroke. Each treated on average only 1 to 2 stroke patients each month. Lack of continuous availability of

support research staff in the hospital for the trial was also cited as an important reason for nonrecruitment. Many paramedics strongly believed that besides increasing researcher cover, another way to increase recruitment would be to allow paramedic technicians to participate in the study (these are professionals who provide support to a paramedic during the assessment, diagnosis, and treatment but are not registered with the Health and Care Professions Council regulatory body).

Difficulty in Organizing Face-to-Face Training Sessions (B6). By providing 22 2-hour training sessions, we were able to train nearly 80 paramedics for the trial[6]; that is, face-to-face training was a time-consuming procedure. The paramedics thought that their shift-working pattern and the requirement to attend in their personal time were obstacles to attending meetings. They believed that future trials could make use of electronic media and DVDs for training purposes and that paramedic team leaders and research champions could help organize local training sessions in each ambulance station, as well as recruit paramedics for the trial.

LIMITATIONS

The study had several limitations. First, it did not include all the paramedics trained for the trial. It is possible that individuals who took part in the qualitative substudy were biased in terms of more favorable views toward the trial compared with those who did not take part. Our main focus was on gathering views and experiences of individuals who did participate in RIGHT in terms of recruiting patients. However, we also included 1 paramedic who did not recruit patients to the study in an attempt to broaden the data.

Second, the substudy was based on post hoc reports by participating paramedics. No doubt further relevant insights could be gleaned by direct observations, but these were beyond the scope of this study.

Third, because interviews were not conducted immediately after recruitment attempts, paramedics may have been affected by recall bias.

Fourth, the researcher (S.A.) was also the coordinator for the main study, and, although he did not have inside knowledge of ambulance services, this may have added bias to the collection and interpretation of data; for instance, the fact that S.A. delivered the training is likely to have influenced the favorable reports about that training.

Fifth, the views and experiences of patients and their relatives would also have added useful insights, but gathering these was beyond the scope of the study.

Nevertheless, the study provides helpful insights and some preliminary recommendations about the feasibility aspects of an ultra-acute ambulance-based paramedic-delivered stroke trial that it is reasonable to argue will have relevance to the future design of such trials. The different research backgrounds (stroke care: S.A., N.S., P.M.W.B.; qualitative research and health care communication: R.P., A.N.S.; and out-of-hospital care: A.N.S.) allowed us to bring varied perspectives to the analysis.

DISCUSSION

The RIGHT qualitative substudy was designed to identify key feasibility issues of an out-of-hospital stroke trial from the paramedic's perspective and to underpin design of future trials in out-of-hospital ultra-acute stroke settings. It was successful in identifying 13 themes (7 about facilitators and 6 about barriers) related to implementing out-of-hospital stroke research. From the perspective of designing and conducting future out-of-hospital stroke trials, we synthesized these themes to produce a series of recommendations for future trial design in relation to paramedic participation in out-of-hospital stroke research, stroke diagnosis, consent, trial processes, trial recruitment, and training, and we discuss these accordingly.

Paramedic Participation in Out-of-Hospital Stroke Research (Themes F1, B1)

Paramedics are integral to the conduct of clinical trials in the ultra-acute stroke setting because patients value their reassurance and professionalism.[20] Studies of UK and US paramedics have noted potential barriers to their participation in stroke research in terms of concerns about ethical and practical challenges, perceived sacrifice of autonomy, and challenge to their identity.[21,22] However, a third of all paramedics in our region participated in training for the RIGHT trial, and the paramedics in this substudy identified several reasons why they thought that participating in research was important. However, lack of institutional support for research time and training was identified as a concern. Interested paramedics should be encouraged to take part in research, and institutions should compensate paramedics for research-related activities.

Stroke Diagnosis (Themes F2, B2)

FAST is well established as a diagnostic screening tool for stroke in the out-of-hospital setting, and paramedics are comfortable using the test in the field. However, there appears to be variation in how it is performed there. Future trials should monitor and ensure standardization of performance of the FAST test to achieve consistency and reproducibility of test results.

Consent (Themes F3, F4, B3)

Paramedics rarely take explicit informed consent from patients in the emergency out-of-hospital setting but understand its importance in research. The limited time for explanation and for patients and relatives to come to terms with the diagnosis were not only identified as barriers to recruitment but also as a hindrance to the effective management of the psychosocial aspects of stroke care. Patients and relatives may have felt pressure to take part in the study initially, although they had the option to opt out later when full consent was sought in the hospital. Difficulties in balancing research objectives with patient care responsibilities are inherent to all health care research, but emergency patients are particularly vulnerable because of the nature of their illness and associated anxiety. However, potential lack of capacity and the short time in which treatments have to

be delivered mean that informed consent is not always possible. The ethical challenges associated with informed consent are not specific to stroke trials but are relevant to all emergency research.[23] This has meant that few randomized controlled trials have been conducted in the out-of-hospital setting[24] and that the majority of treatments currently delivered in this setting are not backed by evidence from research conducted there. The need to identify waiver conditions for informed consent in emergency research is recognized,[18,25] although it can be difficult for out-of-hospital studies to satisfy the current eligibility criteria for the waiver.

In this study, an additional member of the hospital research team sought subsequent informed consent in the hospital, and all patients or relatives, including in cases in which the paramedic had granted proxy consent in the acute phase, opted to continue participation. We recommend this dual consent procedure for future trials. Also, the patients requiring proxy consent (either by relative or paramedic) had more severe stroke and a worse outcome than those able to give their own consent[6] and were thus all the more important to unbiased recruitment.

Because paramedics did not express any concerns in consenting on behalf of patients in this study, future ambulance-based trials should allow proxy consent if they are to include patients with a range of clinical presentations. However, paramedics should have comprehensive training on the principles and practice of informed consent if they are to undertake proxy consent. There should also be opportunities provided for post hoc support, reflection, and feedback for paramedics who have attempted to recruit patients in these challenging circumstances.

Trial Processes (Themes F5, B4)

The trial benefited from the simple packaging of the investigational medicinal product, limited and specific inclusion and exclusion criteria, and brief information and data collection sheets. However, this may also have contributed to the ease with which some trial envelopes were lost when ambulance vehicles were serviced or transferred to a different station.

Maintaining an accurate log of the trial investigational medicinal product is an essential component of any controlled trial and is often done in collaboration with a research pharmacist, often based in the hospital. The absence of research pharmacists in ambulance services and the greater potential for trial packaging to be lost offers particular problems in the out-of-hospital environment. We suggest that future studies explore assigning investigational medicinal products to individual paramedics, although this would be subject to local guidelines and practice. The importance of this aspect of the trial clearly needs including within training and information to paramedics.

Recruitment (Themes F6, B5)

The trial itself was able to achieve just over half of its intended recruitment, and our estimates indicate that only a fifth of eligible patients were recruited into the study. Lack of continuous research cover and the low rates at which paramedics encounter acute stroke were identified as important reasons for underrecruitment. Although most paramedics thought that involving paramedic technicians could improve recruitment, lack of a regulatory license for these staff to deliver treatments may preclude their participation in this type of research. Training greater numbers of paramedics could improve recruitment, although this would present logistic challenges and could mean less-motivated paramedics being trained. Paramedic team leaders and research paramedics could help identify colleagues likely to be active participants, as we did in this study. Paramedic proxy consent as used in this study may allow a further 25% of eligible patients to be recruited.

Training (Themes F7, B6)

Regular and continued training, in a form that helps familiarize paramedics with acute stroke, as well as with trial procedures, is essential because individual paramedics treated only a few stroke patients each month. Moreover, continued training and support in relation to consent procedures, investigational medicinal product, and managing the tensions between supporting patients and their relatives in dealing with the psychosocial issues of stroke while implementing the trial would help paramedics to deal as well as possible with the difficulties of implementing a trial. It would also be ideal to ensure that paramedics not taking part in the actual trial know about it to maximize their cooperation and support.

The shift-work pattern and lack of funded time or "time in lieu" for research in the ambulance service that took part in this study meant attendance at face-to-face training sessions was poor. Besides approaches to maximize such attendance, use of other modalities of training delivery through Web-based platforms, DVDs, or teleconference supported by learning materials delivered through e-mail, posters, or pamphlets should be considered, depending on local circumstances and need.

Last, although all paramedics were asked about trial processes causing delay to hospital admission, this did not emerge as a theme. Transport times were measured and compared, and these were not significantly increased in the RIGHT study; time from paramedic review of the patient to hospital arrival was 50 versus 48 minutes (trial versus nontrial; P=.70).[6]

Ultra-acute stroke research in the out-of-hospital environment is feasible. We were able to identify paramedics who were motivated and keen to take part in research. We found that including the out-of-hospital environment in ultra-acute stroke trials is feasible but that barriers need to be addressed. Individuals planning and conducting out-of-hospital stroke research should seek or work to ensure motivated paramedics, an easy diagnostic stroke tool, and straightforward trial processes. They should also include ways of managing important barriers such as emergency consent process and challenging training circumstances. Allowing proxy consent by paramedics in the

emergency setting may address some of the difficulties with out-of-hospital emergency consent.

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