Randomised trial of clinical and cost effectiveness of Administration of Prehospital fascia Iliaca compartment block for emergency hip fracture care Delivery (RAPID 2)

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1.1	Removed EMAS as site	12.2.21	JJ
1.2	Added ISRCTN and REC details. Clarified inclusion of patients who have died before consent approach in anonymised data. Updated contact details. Removed documents covered section.	25.3.22	MK
1.3	Updated RAPID2 logo. Addition of Levobupivacaine as alternative drug to prilocaine. Update of sites (removed table). Sponsor representative update. Added NIHR disclaimer and funded by logo.	14.04.24	MK

Abbreviations

ASIS	Anterior Superior Iliac Spine
CAG	Confidential Advisory Group
CI	Confidence Interval
CRF	Case Report Form
CTIMP	Clinical Trial of Investigational Medicinal Product
ED	Emergency Department
GCP	Good Clinical Practice
FICB	Fascia Iliaca Compartment Block
GDPR	General Data Protection Regulation
HRQoL	Health Related Quality of Life
IV	Intravenous
KG	Kilogram
MHRA	Medicines and Healthcare Products Regulatory Agency
ML	Millilitre
NHS	National Health Service
PCR	Patient Clinical Record
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
SAIL	Secure Anonymised Information Linkage

Introduction

Background

Hip fractures are very common – approximately 75,000 people suffer one each year in the UK [1]. A hip fracture can be devastating for a patient – there is a high associated short-term mortality, and those who survive are likely to be more dependent and less mobile than before their injury [2-4]. At present, a hip fracture is the most common cause of admission to an orthopaedic ward with an average length of stay of 21 days. Patients with hip fracture occupy 2.5% of all hospital beds at any time and cost the National Health Service (NHS) £2 billion each year [5, 6]. As the average age of the population rises, the annual incidence and cost of hip fractures will also increase. Improving the care of patients with hip fracture is therefore of great and increasing importance.

When a patient fractures their hip, both the event itself and its aftermath are excruciatingly painful [7]. Untreated pain will increase the neuro-hormonal stress response and the risk of delirium [8] but the literature suggests adequate pain relief is often not achieved for patients with hip fracture in the prehospital environment [9-11].

Intravenous (IV) opioids (usually morphine) are most commonly given to patients by paramedics at the scene of their injury [6], but are relatively ineffective for dynamic pain, which a patient is likely to experience during movement to the ambulance and conveyance to hospital [5].
Importantly, opiates can cause numerous serious side effects, including nausea, constipation, delirium and respiratory depression. These may delay surgery, require further treatment and worsen patient outcomes [12].

Long term outcomes of patients with hip fracture may improve if they did not receive opioids in prehospital care. If the paramedic who attends the patient is able to administer an alternative form of analgesia, the patient may not require morphine and thus not be exposed to opiate side effects [13-15]. For instance, if a patient who has received morphine experiences respiratory depression, they may require naloxone and be more likely to suffer from respiratory infections. Alternatively, if morphine causes the patient to be acutely confused, their surgery may be delayed beyond the recommended 48 hours in which it is known to improve outcomes [16-18]. Such events lead to increased costs to the NHS, both directly from treatment required to alleviate the side effect, and from the increased length of hospital stay to do this. Providing alternative, effective, non-opioid pain relief to patients with hip fracture in prehospital care may reduce side effects and improve patients' outcomes including length of hospital stay (as found in an in-hospital study [19]). This would be beneficial for both patients and the NHS.

Fascia Iliaca Compartment Block (FICB) – a local anaesthetic injection directly into the hip region – is routinely used by medical, and increasingly, nurse practitioners in the Emergency Department (ED) and on orthopaedic wards for pain relief. Although this procedure may provide effective analgesia as well as allow the reduction of morphine administration, it is not known whether it is safe, improves patient outcomes or is cost effective in the prehospital setting.

FICB is a suitable alternative to opiate medication; it is a regional anaesthetic technique which delivers local anaesthetic directly to the hip region [20]. In-hospital studies have shown that FICB provides effective pain relief for hip fracture with minimal side effects (fewer than morphine); is inexpensive to provide; and the technique to administer is easy to learn [21-27]. The Association of Anaesthetists of Great Britain and Ireland support its delivery by non-medically trained health professionals [28]. So far, three small studies have been conducted, all demonstrating the viability of delivery of FICB by non-medics in prehospital care: one by nurses [29] and two by paramedics [30, 31]. One of these was a single-site feasibility study, RAPID, conducted by this study team, to ensure that this multi-centre randomised controlled trial (RCT) would be viable in practice and worthwhile conducting [31].

Current prehospital pain relief for patients with hip fracture is inadequate and may be detrimental to patients in the long term. Our proposed research will provide robust evidence as to whether on-

scene paramedic administered FICB for patients with suspected hip fracture is safe and effective in terms of patient outcomes and costs.

We have identified four recent reviews in this area:

- A systematic review (Ritcey et al 2016) of regional nerve blocks for hip and femoral neck fractures in the ED including nine randomised controlled trials concluded that regional nerve blocks may be superior to traditional analgesia for patients with hip fractures [32]. They found a significant decrease in opioid usage in five out of six studies that used opioids as a control – an effect which was maintained in the two double-blinded studies. None of the studies reported any immediate life-threatening complications of nerve blocks, but the authors did not draw conclusions about whether a reduction in opioid consumption led to reduced complications 'due to under-reporting of complications in the majority of studies'. Limitations cited by the authors were: the risk of publication bias (smaller, negative studies may have gone unpublished); the quality of the evidence (moderate to high risk of bias); and clinical heterogeneity (different standard pain control).
- A narrative review (Scurrah et al 2018) of regional nerve block for early analgesic management (preoperatively – in prehospital care, in the ED and in the anaesthetic bay prior to surgery) of elderly patients with hip fracture, included eight RCTs. It concluded that nerve blocks such as FICB for the elderly hip fracture patient should be integrated into routine acute pain management protocols as they reduce acute pain, the need for opioids, and the incidence of delirium; and may benefit patients in terms of morbidity, mortality and quality of life [33].
- A literature review (Amin et al 2017) of nerve blocks in the care of geriatric patients with hip fracture stated that the routine use of preoperative nerve blocks for hip fracture may improve patient outcomes, given the unacceptably high morbidity and mortality associated with opioid use [34]. They concluded 'localized nerve blocks, specifically FICB, have been shown to be safe and effective in managing acute hip fracture pain in geriatric patients, leading to decreased opioid use'.
- A summary of a systematic review and meta-analysis (Fadhlillah and Chan 2019) of efficacy and safety of FICB in the acute preoperative pain management of hip fractures including eight RCTs concluded that FICB was superior to systemic analgesia in controlling acute pre-operative pain in patients with hip fractures and was pharmacologically safe, with fewer side effects reported in the FICB arms. The analgesic benefits of FICB were more evident during mobilisation of the limb (on dynamic pain) [35].

Most studies included in these systematic reviews were carried out in EDs, with only a minority in the prehospital setting. Studies generally involved small numbers of patients, and meta-analysis is challenging due to heterogeneity in interventions (other types of nerve block are included besides FICB) and outcomes. The reviews all call for further definitive research in the area – our proposed RCT is therefore required to provide robust evidence to inform policy and practice.

In our completed RAPID feasibility trial (funded through Health and Care Research Wales Research for Patient and Public Benefit funding stream, Award 1003), we trained 19 paramedics in the catchment area of one receiving ED within the Welsh Ambulance Service to administer FICB. They randomly allocated 71 patients to trial arms. Thirty-one out of 35 participants randomly allocated to the experimental arm consented to follow up, whilst 26 out of 36 participants randomly allocated to receive usual care consented to follow up (overall consent rate of 80%). Of the 31 participants followed up in the experimental arm, 17 received FICB (55%). Significantly fewer patients received morphine in the experimental arm, 13/31 (42%) patients, compared to 21/26 (81%) in the usual care arm; a mean difference of -39% (95% Confidence Interval -62% to -16%). The number of patients who experienced Serious Adverse Events (SAEs) was balanced between trial arms – three in the experimental arm and four in the usual care arm. Paramedics recognised hip fractures with reasonable accuracy – a sensitivity of over 75% and a positive predictive value of over 80%. The qualitative component of the feasibility study revealed that paramedics thought FICB was a suitable intervention for them to deliver, within their capabilities and in alignment with current practice. Most patients interviewed could not remember the treatment they received from

paramedics, although those who were aware of receiving the block because of what they were subsequently told said they were happy with the intervention.

We met all predefined progression criteria relating to: 1) the accuracy of recognition of hip fracture by paramedics; 2) the willingness of both patients and paramedics to participate in the study; 3) paramedic compliance with the FICB protocol; 4) the acceptability of FICB as method of providing pain relief in prehospital care of patients with hip fracture; 5) the ability to retrieve outcomes; and 6) the safety of prehospital FICB. We now propose to conduct a fully-powered RCT to test the safety, clinical and cost effectiveness of paramedic-provided FICB for patients with hip fracture at the scene of their injury.

Aim

Our aim is to test the safety, clinical and cost-effectiveness of paramedics providing FICB as pain relief to patients with suspected hip fracture in the prehospital environment.

Trial Design

RAPID2 is a multi-site, parallel group superiority randomised trial with an allocation ratio 1:1. RAPID 2 is not a Clinical Trial of Investigational Medicinal Product (CTIMP) because the efficacy of local anaesthetics and indeed FICB has already been established. This was established with the MHRA for the purposes of the RAPID feasibility study.

Methods

Study Setting

The trial will be conducted in the prehospital environment in the catchment areas of five receiving hospitals by paramedics from the local ambulance service. We have received expressions of interest from ambulance services and partner hospitals across the UK, including East of England, Isle of Wight, South East Coast, South Central and Wales. Each of the potential sites has a large enough volume of patients with hip fracture annually in order to meet our required sample size. Data will be collected from both the ambulance services and receiving hospitals. There will be a Principal Investigator for each ambulance service and each receiving hospital.

Eligibility Criteria

Our target population is patients with suspected hip fracture who are attended by emergency ambulance paramedics in response to a 999 call.

Inclusion for randomisation:

Adult patients attended by a participating study paramedic following a 999 call who are:

- assessed as having an isolated hip fracture – hip fracture assessment checklists will be provided to aid recognition, as in the feasibility study
- conscious (Glasgow Coma Scale Score of ≥ 13)
- haemodynamically stable
- to be conveyed to a participating receiving hospital

Exclusion prior to randomisation:

Patients who

- are taking anticoagulants
- have a hip prosthesis on the affected side
- refuse analgesia
- are thought to be having a stroke
- are combative
- are attended by a paramedic working alone

Interventions

Paramedic recruitment
We will advertise the trial in each participating ambulance service using email, Twitter, the intranet and posters. Paramedics will be advised to contact the local site researcher to sign up for training.

Paramedic training
Paramedics will need to have successfully completed training in order to administer the FICB. Letters of access will be arranged for paramedics to conduct training on hospital grounds. We will follow methods used in the RAPID feasibility trial for this, with the addition of 'scenario training' added to group sessions (as suggested in the qualitative work conducted with paramedics during the feasibility study); familiarisation with the trial packs and methods; and refresher training midway through the recruitment period in order to prevent skill decay. The decision to add these elements was due to the results of the qualitative focus groups in the feasibility study, as paramedics suggested ways to improve the training [36]**.**

The three elements to the initial paramedic training are:

1. Online 'e-learning'
   We will train paramedics using an online 'e-learning' package, including a video showing the administration of FICB, made specifically for the feasibility study and still fit for purpose. This will be hosted on the paramedics' Electronic Staff Record, which allows monitoring of who has completed the training, or a similar online platform. Paramedics will also complete online Research Governance Awareness Training for prehospital staff, which is specifically designed for paramedics taking part in clinical trials and includes principles of Good Clinical Practice (https://www.neas.nhs.uk/our-services/research-and-development/research-training).

2. Group 'classroom' sessions
   Online training will be followed by group sessions led by a consultant anaesthetist at the receiving hospital to cover: recognition of hip fracture; anatomy relevant to FICB; pharmacology of local anaesthetics; the procedure and equipment required; local anaesthetic toxicity recognition and management; and scenarios relevant to the prehospital environment. Life-sized mannequins, custom made for training paramedics in the feasibility study, will be used to simulate administering FICB. These contain materials to replicate the feeling of the two fascial layers that the clinician will feel resistance from and then a 'pop' when they push through it (referred to as the 'double pop' technique).

   A study site researcher will be present at the group sessions to provide training in trial methods, including trial eligibility criteria, the importance of recording pain scores and the use of scratchcards and randomisation log, adapted to each site to take account of local practices.

   In the context of the COVID pandemic, these training sessions may also need to take place online. We will be guided by government guidelines at the time.

3. In-hospital training
   Pairs of paramedics will then attend sessions at the receiving hospital where they will administer FICB to real patients, supervised by an anaesthetist. (We will arrange letters of access for this purpose). They will alternate between administering and critiquing the FICB to ensure their learning is active [37]. The paramedics must administer three FICBs competently before being allowed to recruit patients to the study. Suitable emergency hip fracture patients will be identified from trauma theatre lists; the ED; and post-op wards. There may also be opportunity for paramedics to administer FICB to elective patients undergoing hip replacement. The FICB and Intralipid (antidote for local anaesthetic toxicity) packs will be available for paramedics to familiarise themselves with and the anaesthetists providing training will run through prehospital scenarios with the paramedics, including assessing eligibility and taking consent.

   Taking into account that this element of training is opportunistic and requires suitable patients, we will provide written material and assessments related to trial methods to optimise learning

in between block performances. The written assessments will include both research and clinical questions, including, for example: patient trial eligibility; contraindications to FICB; information to give when taking consent for FICB including risks and how long the FICB will take to work.

We will make all written material and presentations used for training available in an online area, such as Dropbox, accessible to all the training paramedics.

Formal refresher training will be available to any paramedics who have not performed FICB for more than three months.

Information sheets will be provided to all untrained operational staff (paramedics, advanced paramedic practitioners and emergency medical technicians) in the participating areas of ambulance services so that front line staff are aware of the trial and have an acceptable understanding of it. This decision is based on qualitative results from our feasibility study; paramedics felt much more confident when working with other trained paramedics able to help them. They thought that colleagues should be made aware of the purpose of the trial and the role of study paramedics, so that they could help in simple ways such as drawing up the local anaesthetic.

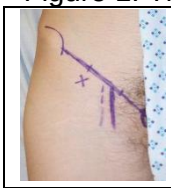
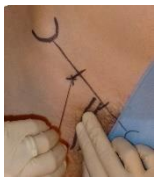
Usual care
Currently, when a patient who has called 999 is attended by a paramedic for a suspected hip fracture, the paramedic clinically assesses the patient, takes their history, examines them and records observations (blood pressure, heart rate, respiratory rate, oxygen saturations, Glasgow Coma Scale, patient reported pain score and temperature). Paramedics cannulate patients and provide IV fluids and/or oxygen, as appropriate, based on clinical parameters. They are currently able to provide systemic analgesia only, most commonly opioids (IV morphine), paracetamol and Entonox. In RAPID 2, patients allocated to usual care, will receive this care.

Intervention care
If the patient is randomly allocated to the intervention arm, the paramedic will administer FICB in addition to basic usual care as described above, but avoiding use of opioids. The FICB will utilise 1% Prilocaine or Levobupivacaine 0.25% and will follow the method used in the RAPID feasibility study (based on Dalens et al 1989) [20]. The paramedic will still provide the patient with paracetamol and Entonox but should not give the patient morphine for at least 20 minutes after the patient has received the FICB (to allow for the time of onset of Prilocaine/Levobupivacaine). If, however, the FICB does not relieve the patient's pain after 20 minutes, the paramedic would be able to give the patient morphine if judged appropriate ('rescue morphine').

In order to provide FICB to a patient allocated to the intervention arm, the paramedic will:

- assess for any contraindication to FICB
    - Body mass apparently less than 50 kg
    - Pregnancy
    - Allergy to local anaesthetic
    - Neurovascular damage to the affected leg
    - Infection at the site of injection
    - Previous femoral bypass surgery
    - Inability to palpate the femoral artery on the affected leg
- explain the risks and benefits of FICB
- take verbal consent for the procedure
- move the patient into a suitable position to administer the FICB
- follow the treatment protocol for delivery of FICB – see Figure 1.

Figure 1: Treatment protocol for delivery of FICB

 Place one middle finger on Anterior Superior Iliac Spine [ASIS] and the other middle finger on the symphysis pubis. Divide the line using both index fingers into three equal parts as shown
Mark the injection point 1cm below the lateral index finger
 Confirm the femoral artery position is medial to the injection point (palpate femoral artery making sure it is at least 2cm medial to marked injection point)
Wash hands, prepare equipment and the sterile field: ▪ Open dressing pack, syringes, needles, local anaesthetic etc ▪ Clean the skin from the ASIS to the pubic bone with provided skin preparation ▪ Wash hands ▪ Put on sterile gloves ▪ Draw up prilocaine 1%/Levobupivacaine 0.25% into 1 x 20ml and 1 x 10ml syringe and flush the extension line ensuring Bsmart pressure monitor positioned between syringe and needle.
Insert the 18 gauge block needle perpendicular to the skin at the marked point ➢ **Do not aim needle medially**
Advance the needle ▪ Advance through **two distinct pops** [loss of resistance felt following penetration of Fascia Lata and Fascia Iliaca] ▪ If pop not clear, bring needle back under skin and slightly change angle ▪ Once in position, the needle can be released
Aspirate and if no blood detected: ▪ Slowly inject Prilocaine 1% or Levobupivacaine 0.25% x 20ml total aspirating every 5 mls ▪ There should be no resistance to the injection. The Bsmart monitor should not progress into the yellow zone; if there is, pull back cannula slightly and retry injection Correct placement is confirmed by: ✓ No resistance to injection ✓ No appearance of subcutaneous swelling ✓ Onset of analgesia over 20-minutes
Change syringe and complete Prilocaine/Levobupivacaine injection according to patient weight (total dose 30ml if >50kg body weight). Remove cannula
Monitor and record patient observations over first 30-minutes NB The biggest risk of local anaesthetic toxicity is during the first 20 minutes following bolus administration

Outcomes

We will compare between trial arms:

Primary outcome: change in patient-reported acute pain from initial paramedic assessment (pre-randomisation) to triage nurse assessment on arrival at ED

Secondary outcomes during initial care and up to four months:

•Routine data

- ambulance service job cycle time (from 999 call to 'ambulance free')
- analgesia and anti-emetics administered prehospitally, including morphine and 'rescue morphine'

- length of stay in hospital, ITU and residential rehabilitation care following injury
- subsequent ED attendances and emergency admissions
- mortality
- diagnosis (for patients who did not have a hip fracture)
- where patient was admitted from and discharged to

•Patient reported outcomes

- satisfaction with care (Quality of Care Monitor at one month)
- health related quality of life (HRQoL) (EQ-5D-5L at one and four months)
- mobility (Rivermead Mobility Index at one and four months. One question will be removed to enable to patient to complete the questionnaire by themselves)

•Costs to the NHS

Participant Timeline

Day 0 – Participant randomly allocated to trial arm and receives experimental or usual care

Day 0 – Day 7 – Participant will be monitored for SAEs

By Day 10 – A trained NHS researcher will make contact with the participant to explain that they have been recruited to a research trial; seek the participant's consent for questionnaire follow up; offer the chance to dissent from anonymised routine follow up; and to answer any questions the participant may have.

Day 28 – Participant receives a study questionnaire which includes:

a) Quality of Care Monitor
b) EQ5D5L
c) Modified Rivermead Mobility Index

Day 120 – Participant receives a study questionnaire which includes:

a) EQ5D5L
b) Modified Rivermead Mobility Index
c) £10 High Street Shopping Voucher

Sample Size

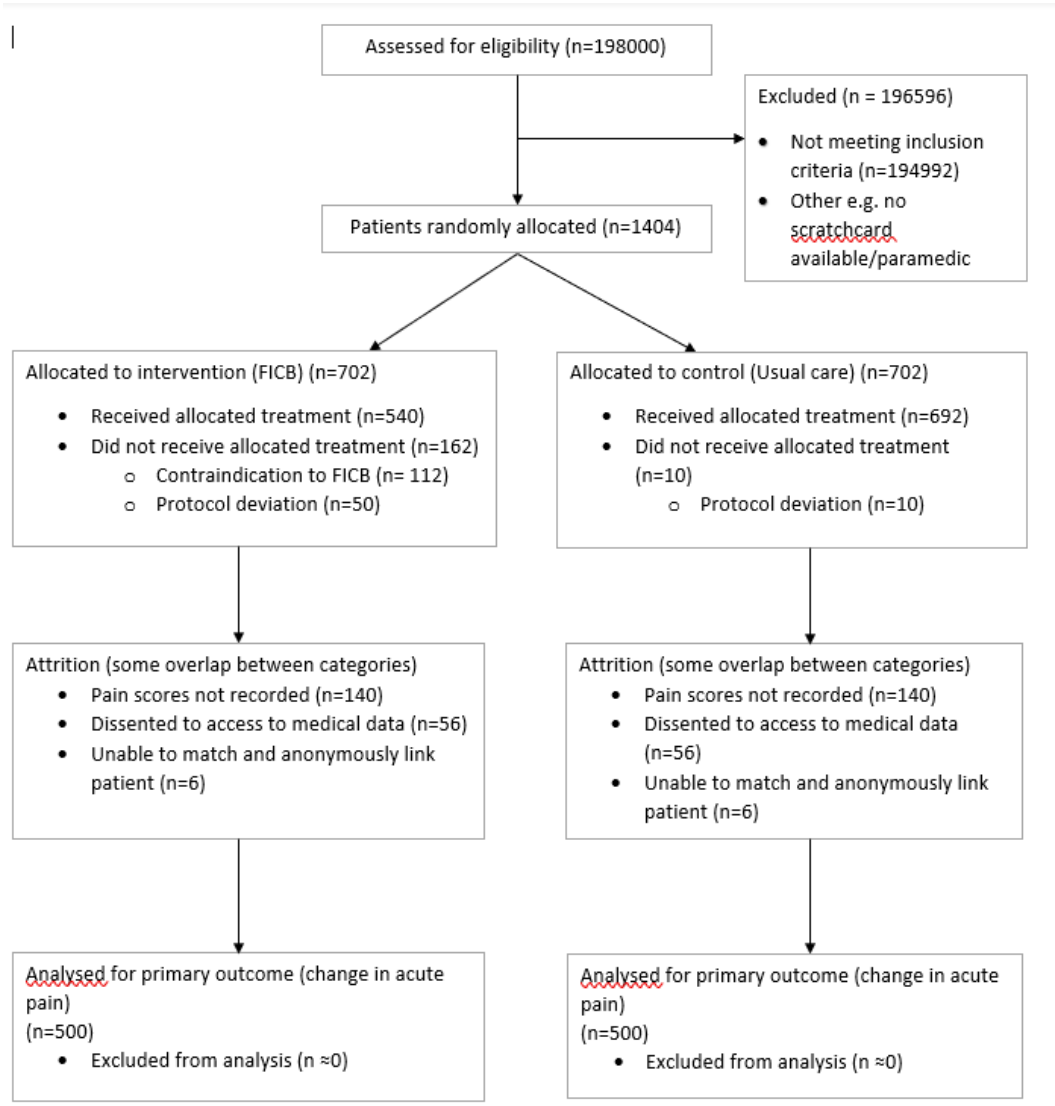
Our feasibility study used an 11-point scale (0 being no pain, 10 being the worst pain imaginable), and reported an average reduction of approximately 4 points in pain score recorded pre-randomisation, albeit with considerable variation; the standard deviation is approximately 2.7 points. This data is consistent with that reported elsewhere in broadly similar settings [38]. Our patient and public representatives and clinicians judge an average difference in change of 0.5~0.6 points to be clinically important, both to patients and to commissioners making decisions on whether this intervention is worth funding. The mid-point of this range in average differences in change corresponds to a standardised statistical effect of ~0.2 between control and intervention arms; for 90% power at the 5% significance level, we therefore need approximately 1000 analysable outcomes. If approximately 20% of patients lack pain scores; 10% of participant dissent from anonymised follow up of routine records; and we are unable to match 1% of cases in Secure Anonymised Information Linkage (SAIL) and NHS Digital, then we will need to allocate randomly and equally 1404 patients to study arms.

The rate of recruitment of 5 patients randomised per paramedic per year observed in our feasibility study will be reduced by the addition of an exclusion criterion (the use of anticoagulants); our data indicates that the reduction is likely to be ~30%. With this reduction, we have calculated that we will need five collaborating sites with approximately 40 trained paramedics recruiting an average of seven patients in 24 months. Each site will be expected to recruit approximately 280 patients in this time, although there may be slightly different recruitment rates between sites due to the different demographics and sizes of catchment areas of receiving hospitals. We will monitor

recruitment particularly closely in the first six months of the trial (pilot phase) to see if these targets are realistic, so that we can take action as early as possible to rectify any problems identified. Although we expect that 40 paramedics are required in each site to meet our recruitment target, we will train 10% more at each site to account for attrition (due to maternity or sick leave, secondment, or career change or progression) in study paramedics.

Recruitment

Projected CONSORT flow of participants



Pilot phase

We will determine whether to continue patient recruitment based on whether stop/go criteria are met during the first 6 months of recruitment. The following thresholds will be presented to the Trial Steering Committee for approval at the outset of the trial.

Recruitment metric	Red	Amber	Green
Recruitment rates (% of target recruitment)	<64%	65 – 84%	>85%
Recruitment rate/site/month	<7	7 – 10	>10
Number of sites opened	3	4	5
Total number of participant recruited	<210	210 – 300	>300
Dissent rates	>20%	11 – 20%	<10%
Paramedics' recognition of hip fracture (false positive rate)	>30%	20 – 30%	<20%
Difference between groups in SAEs	>20%	10 – 20%	<10%

Allocation (sequence generation, concealment and implementation)

The trial statistician will produce a randomisation schedule, stratified by site and paramedic, with allocations concealed on scratchcards. The schedule will ensure that each paramedic's pack of ten scratchcards (issued with unique and consecutive serial numbers) contains at least one allocation to FICB, but it will not necessarily have equal numbers of intervention and control allocations, thereby precluding, at any stage, advance and certain knowledge or prediction of remaining allocations.

With a maximum of 44 paramedics per site, we will produce 2400 scratchcards, and issue these in packs of ten. For eligible patients, paramedics will scratch the card's panel to reveal 'Intervention – FICB' or 'Control – usual care' out of the sight of the patient. As we will use the scratchcard serial number as the basis of the patient's study ID, the paramedic will retain the scratchcard in order to store it with the Randomisation Log at their ambulance station, so that the site researchers can monitor recruitment.

Site researchers will conduct an audit of scratchcards at intervals during the recruitment period, and again at the close of recruitment. The use of scratchcards in the feasibility study has been published as a short report in the Emergency Medicine Journal [39], and a picture of the scratchcards used in the feasibility study can be seen below (Figure 2).

Figure 2: RAPID scratchcards image

Blinding

Given the nature of the intervention, it would not possible to blind paramedics or patients to the treatment they received as sham FICB would be unethical [40].

To reduce the risk of bias in reporting pain scores, clinical staff will be blinded to the patient's allocation when recording pain scores:

- the paramedics will be instructed to record the patient's baseline pain score before randomisation
- the triage nurse in the ED will be instructed to take the second pain score at handover, before the paramedic reveals which arm of the trial the patient was allocated to

Data Collection

Routinely collected data:

We will use routinely gathered data wherever possible.

1. *Data related to index event and episode of care:* Site researchers will collect prehospital data for all patients from their Patient Clinical Record (PCR). This will include pre-randomisation patient reported pain score; job cycle time (from first 999 call for the incident to time ambulance reported free to respond to next 999 call); medications given (i.e. anti-emetics and analgesia – FICB, paracetamol, Entonox and morphine); any immediate complications of analgesia given. The researcher will collect data from the ED, most importantly pain score on arrival there. The researcher will check local incident reporting mechanisms (for example, Datix) for any Serious Adverse Events. We are particularly interested in adverse events which may be due to the FICB being performed in the prehospital environment, for example, an increased incidence of infection at the injection site. The researcher will also collect information about any complications of the FICB from the patient's medical notes; and how long the patient waited to be taken to theatre for surgical fixation from the hospital's theatre system. We will record data regarding the patient's diagnosis, so that we know what injury the patient did have, if not a hip fracture. Each site researcher will be given training and guidance notes on completion of the Case Report Forms (CRF). We will monitor completion rates and report back to local teams. All data collection, handling and storage will be compliant with GDPR. We will train, monitor and support paramedics and triage nurses in ED to complete pain scores as reported by patients. Although routine completion rates can be low, they have been shown to be amenable to quality improvement measures e.g. Royal Surrey and partner Trusts achieved an increase from 20% to 95% following an audit and quality improvement exercise (HW, personal communication). We have included costs to ensure that training and support is offered at the outset and throughout the trial at all study sites.

2. *Patient reported outcome measures:* We will send questionnaires to patients at one and four months by post (unless they are still in hospital, in which case they can be completed face to face). Patients will be telephoned approximately three days after they have been sent the questionnaire to ask if they would prefer to answer the questionnaire over the telephone or send back the questionnaire. If we do not receive the questionnaire from the patient three weeks after sending it, and we have not been able to complete the questionnaire over the telephone, we will send one reminder letter to the patient. Questionnaire responses will allow us to compare patient satisfaction (Quality of Care Monitor), HRQoL (EQ-5D-5L) and mobility (Rivermead Mobility Index) between patients in each arm of the trial. Before contacting patients, we will check records to ensure that the patient has not died to avoid causing distress to their families, as well as to record patient mortality. There will be a space on the questionnaire to indicate whether it has been completed by the patient or by a carer/relative, so that outcome data can still be collected for patients with cognitive impairment. Patients will be sent a £10 High Street Shopping voucher with the four month questionnaire as an incentive, which has been shown to increase response rates [41, 42].

3. *Anonymised linked outcomes:* We will link CRF and patient reported outcome data to nationally held routine data through NHS Digital (in England) and NWIS (in Wales) using the split file technique [43] so that no identifiable data are held by the central Swansea Trials Unit team. Trial data will be stored and securely available for analysis in the SAIL Gateway. We have successfully used this approach several times before e.g. SAFER1, SAFER 2; PRISMATIC. [44, 45].

We will request individual level data on previous hip fractures (up to five years before recruitment) from records held within SAIL/NHS Digital, and use these to define appropriate baseline covariates for statistical models when making adjusted comparisons between trial arms. Subject to appropriate ethical, research and information governance permissions, we will also request data on secondary outcomes related to: diagnoses; disposition from ED; length of stay at index episode in hospital, ITU and residential rehabilitation ward; further ED attendances and emergency admissions total length of stay and deaths up to four months.

Our outcomes and measurement intervals match those used in the National Hip Fracture Database (NHFD) as far as possible, but it is important to note that our population will be different, as approximately 20% of our participants may not have a hip fracture

Monitoring for false positives:

The positive predictive value of the paramedics' diagnoses of hip fracture in the feasibility study was slightly lower (80.7%) than desirable in practice. Therefore, we will monitor for false positives and discuss these with paramedics on a regular basis to ensure that they are aware of incorrect diagnoses and are able to learn from them.

Health economics:

The health economics strand embedded within RAPID2 includes three interlinked aims: a) to cost the intervention; b) to measure patient's NHS resource use from baseline to end of follow up; c) to determine the value for money of the new model of care via Cost Effectiveness Analysis (CEA), Cost Utility Analysis (CUA) and Cost and Consequences Analysis (CCA) [46].

Intervention costs: This includes all the costs (excluding research costs) sustained to deliver the intervention. A purposely designed data collection questionnaire tested in the feasibility study will be sent to each recruiting site to retrieve the following information:

- Time spent on online training measured by the time spent by the health professionals to cover the online module and costed according to their pay scale
- Time spent face-to-face training sessions measured by the time used to run the sessions and costed according to trainer and the trainee's pay scale
- Time spent for travelling measured by the amount spent by either the trainer and/or the trainee to in travelling in order to attend the face to face training sessions and costed according to the pay scale of the person sustaining the travelling
- Travelling expenses costed mainly by fuel and fare tickets purchased
- Specific equipment needed for the training (e.g. groin model)
- FICB packs including anaesthetic agent and Intralipid (antidote for local anaesthetic toxicity)

Formal refresher training will be recorded and costed in a similar manner. Compared to the feasibility study, the detailed costing of the intervention will benefit from the multi-centre nature of the study and give a more representative picture of NHS costs for wider implementation of the new treatment.

NHS resource use: Data sources on NHS resource use in follow up comprise the CRF validated in the RAPID feasibility study and routine data. From these we will retrieve the following information: hospital stays, hospital-based treatments, readmissions, ED attendances, Aes (e.g. Deep vein thrombosis), Ars (e.g. Infection), SAEs (e.g. Pneumonia), SUSARs (e.g. Femoral nerve damage), prescription of non-opioid analgesia (including FICB administered by paramedics), prescription of opioids, prescription of anti-emetic. Resource use will be costed using appropriate unit cost data (Unit costs of health and social care, Personal Social Services Research Unit, NHS reference costs, Department of Health, British National Formulary). The feasibility study also demonstrated that paramedic time with the patient was similar in the two study arms; we will therefore use a national average cost figure to cost ambulance attendance. In adherence with the principles set by the FORGE group [47] we will not collect data on GP visits since these would constitute a small cost compared to the other resources and considerably increase the burden on the respondents especially because the study population includes a large proportion of elderly people who are likely to be on multiple medications. The collection of primary and social care data will be collected only when available routinely from validated sources.

Outcome measures for CEA and CUA: The data collection process of Pain scores and EQ-5D-5L is reported in the subsection on routine data collection.

Data Management

Data on CRFs will be entered onto REDCap at each site. There will be range checks put in place on REDCap for certain data values to minimise errors e.g. only dates within the recruitment period can be used for date of randomisation. Quality assurance checks will be carried out on 10% of the data inputted at each site. If any errors are found, that site's data entry will be checked in full.

At the end of the recruitment period, identifiable and clinical data in split file format will be exported to NHS Digital (England) or NWIS (Wales) by research support staff to be anonymised, and then exported into the SAIL (Secure Anonymised Information Linkage) databank for secure storage and analysis via the SAIL gateway (33). Irreversibly anonymised data such as these are not considered personal data under the General Data Protection Regulation (GDPR; EU Regulation 2016/679). However, until the data are exported and anonymised, we will include instructions on how to dissent from the study prior to data export when the NHS researcher approaches the patient to discuss the trial up to ten days after their injury. This will mean that participants will have until the end of the recruitment period to contact research support staff to request their data not be made available to the study team.

We will store SAE data separately from the rest of the trial data, as we will report safety for all randomised patients.

Statistical Methods

Data Linkage Process
Identifiable data relating to trial participants will be gathered at source from within the participating ambulance services and ED. The trial team will support each service to provide split files (separating identifying from clinical information) to NHS Digital (England) and NHS Wales Informatics Service (Wales), where individuals' records will be matched to central NHS administrative records. Participants will be allocated Anonymised Linking Fields (ALFs) and their clinical records from ED, inpatient and ONS databases will be linked without breaking confidentiality. Files with outcomes and unique study identifiers will be combined to form a single, integrated study dataset, available for analysis in the SAIL Gateway – an NHS Digital-recognised 'safe haven' for linked data. We have tried and tested this methodology in emergency and primary care trials and have recently published results of the SAFER 2 trial, which included anonymised linked outcomes (ED, inpatient and mortality) on >4,500 patients attended by paramedics in three UK ambulance services [48].

Data analysis
The primary analysis will be by 'treatment allocated'; adjusting for explanatory factors and covariates including patient age and gender, patterns of presentation (eg, whether out-of-hours or not) and previous hip fractures. Generalised multilevel mixed linear models will accommodate clustering effects for paramedics and study sites, with numbers of levels in models determined using statistically significant changes in likelihood ratio tests according to the principle of parsimonious parameterisation. Residual diagnostics will be used where analyses assume Normality; if the distributions of residuals are markedly non-normal (eg: marked skewness in the primary pain outcome), data transformation techniques or bootstrapping will be considered. Residual analysis will also be used to identify outliers; identified outliers will be excluded before repeating the analysis.
Interim analyses will be conducted at X months.

Health economic data analysis
The health economic analysis, also by treatment allocated, will be carried out in line with the NICE guidelines on health technology appraisal and presented in accordance to the CHEERS checklist [49]. Management of missing and non-normally distributed economic data will follow the principles outlined above.

Analysis of training costs: An average cost per person trained will then be determined by dividing the total cost of the training by the number of attendees. The cost per patient treated will be determined by dividing the training cost by the likely number of eligible patients seen by each ambulance unit trained. Training is a capital investment with a 5-year life expectancy and, as such, the cost will be annuitized (using 3.5% discount rate) to determine the cost per year.

CEA and CUA: We will conduct two main analyses of incremental cost-effectiveness to estimate the incremental cost per unit change in pain score from that recorded pre-randomisation to that recorded on arrival in ED. Compared to hospital setting (both ED and ward), pain is relatively rarely used as a primary outcome measure in the pre-hospital setting. This large multi-centre study will offer some useful insights into its use as an outcome measure in this setting. We again use mixed linear models to estimate the cost effectiveness ratios and employ non-parametric bootstrap estimates (bias corrected) to confirm 95% confidence intervals. A cost effectiveness plane will present the probability that the intervention is dominant or cost effective. If FICB is more effective but also more expensive the Cost Effectiveness Acceptability Curves (CEAC) will show the probability of effectiveness against different thresholds of willingness to pay for pain reduction [50].

The incremental cost utility analysis will assess the cost per quality-adjusted life years (QALYs) of the new model of care. In the UK, the National Institute for Health and Care Excellence (NICE) recommends the use of Quality Adjusted Life Years (QALYs) as a measure of health benefits and the use of the generic preference-based HRQoL measure EQ-5D-5L to determine health status. HRQoL appears to be sensitive to change and appropriate for use in orthopaedic patients [51-54]. Again, mixed linear models will be used to estimate the cost utility ratios and bias corrected non-parametric bootstrap are used to confirm 95% confidence intervals around the point estimate. We will use baseline EQ-5D-5L scores as a covariate in the estimation of QALYs.

A series of sensitivity analyses, involving NHS cost drivers and training formats, will assess the robustness of both incremental cost effectiveness analyses.

Cost and consequences analysis: In this analysis costs are set against the all range of outcomes (primary and secondary). This framework of analysis is now recognised as a useful alternative by NICE when carrying out economic evaluation with multiple important outcomes, interventions that have multiple effects which are difficult to summarise in a common unit such as public health intervention (NICE 2013) and the preferred framework for the economic evaluation of public health interventions. Because CCAs are not restricted to a single outcome measure the use of this framework will enable us to focus the attention of policy makers to the set of secondary outcomes we are measuring in this study [55].

We will formalise, and agree with trial management and oversight committees in advance of any analysis, all planned analyses in a combined Statistics and Health Economics Analysis Plan (SHEAP), compliant with relevant Swansea Trials Unit Standard Operating Procedures. The SHEAP will provide full details on model fitting conventions, such as inclusion and exclusion rules for covariates and factors, management of missing data, and the reporting of outcomes. In summary: potential factors and covariates to be included in models will be tested; those with an F value of less than 1 (that is, they increase the standard error of the estimate) will be excluded and the analysis recalculated. Binary covariates where almost all cases (>90%) are in one category will also be excluded. Wherever possible, outcome descriptions, summaries and comparisons will be reported using appropriate CONSORT guidelines, including estimates with 95% confidence intervals (allowing two-tailed tests at the 5% significance level).

Data Monitoring

A Data Monitoring Committee (DMC) will be formed, to include (one of whom will act as Chair):

- Two patient and public representatives
- Statistician
- Clinician – anaesthetist and either orthopaedic surgeon or orthogeriatrician

- Paramedic

The DMC will monitor study data at interim periods and make recommendations to the Trial Steering Committee (TSC) on whether there are any ethical or safety reasons why the trial should not continue. Its members will have access to comparative data and interim analyses and may request the un-blinding of such data at any time. The DMC will also consider requests for the release of data. The DMC may be asked by the TSC, Trial Sponsor, or Study Funder to consider data emerging from other related studies. If new evidence becomes available during the course of the trial, it is the responsibility of the trial and/or Data Manager to provide that information to the DMC to allow them to consider such issues and make recommendations on the continuation of the trial to the TSC.

Serious Adverse Events

We propose to monitor adverse events in all randomised patients up to one week, to assess them for seriousness and to investigate all Serious Adverse Events (SAEs) to establish whether they are a reaction to the treatment received. We will report all Suspected Unexpected Serious Adverse Reactions (SUSARs) promptly to the sponsor and Chair of the DMC. We will report SAEs regularly to the Trial Management Group (TMG), TSC, DMC and Sponsor.

Any adverse event that is defined in the Prilocaine or Levobupivacaine Medicine Information Leaflets will; be regarded as expected. Adverse events recorded in the safety reporting Datix systems for ambulance service and hospital or in routine hospital notes will be noted and assessed by a member of the direct care team (Research Nurse or Principal Investigator, receiving hospital). Based on consensus of the clinicians involved in the feasibility study, these events will include (but not be confined to): chest infection; sepsis; ITU admission; requirement for blood transfusion; fall in hospital; drug errors; psychotic episode; nerve damage; and local anaesthetic toxicity.

We will capture harms beyond this period through the outcomes agreed for the trial which include mortality, length of stay and readmissions, self-reported quality of life and mobility.

This approach reflects information on the harms captured in the feasibility study - the number of patients who experienced SAEs was balanced between trial arms; three in the experimental arm and four in the usual care arm. One patient in the experimental arm experienced local anaesthetic toxicity (successfully treated by the attending paramedic with Intralipid without any long term sequelae); a further patient in this arm died within seven days of their hip fracture due to community acquired pneumonia; and one further patient in this arm had sepsis and bowel obstruction whilst under palliative treatment for metastatic cancer. In the usual care arm: one patient had rhabdomyolysis requiring dialysis and intensive care admission; two patients died within seven days of their injury, one due to heart failure and the other due to pulmonary oedema; and one patient required a blood transfusion. Only one SAE was judged to be directly related to the intervention (local anaesthetic toxicity).

Auditing

Site monitoring visits will be conducted at all sites at least four times during the recruitment period (approximately once every six months) by a member of the trial – namely by the Chief Investigator and / or Trial Manager.
Scratchcards will be audited at least four times during the recruitment period (approximately once every six months). This will be to ensure that they are being used in numerical order and the silver panels are not being tampered with.

Ethics and Dissemination

Research Ethics Approval

We successfully gained ethical and research development approvals for the RAPID feasibility study; we therefore do not expect any major causes for concern in this respect. However, the ethical issues for consideration, as included in our application for ethical approval in RAPID are as follows:

1. Clinical risk – FICB carries a low risk of complications including allergic reaction to local anaesthetic; infection at the site of injection; injection into blood vessel; nerve damage; local anaesthetic toxicity; failure to provide analgesia; and further injury as a result of the leg being numb. There is also a risk of misdiagnosis and thus inappropriate application of FICB (in a patient without hip fracture). In this trial we will reduce this risk by using a checklist to support diagnosis; by providing thorough training and competency testing; and by using a relatively short acting local anaesthetic. There is also a risk of sharps injury, though we do not believe this will increase a paramedic's pre-existing risk and have excluded combative patients from the trial to ensure this.

2. Consent – In this RCT in the emergency prehospital setting, we do not propose to attempt to consent patients to participation in research at the time of their injury, as they are likely to be in significant pain. We believe that truly informed consent to research cannot be gained in this highly emotional and distressing situation. We propose that paramedics consent patients to treatment only, and that an NHS researcher approach the patient for consent to follow up in research questionnaires within ten working days of the 999 call.

3. Carrying out research with patients with cognitive impairment – We expect a significant proportion of participants in RAPID 2 to have cognitive impairment and lack capacity to give their own informed consent. We do not propose to exclude these patients from the trial, as the evidence we gather in this group may contribute to improving their care and outcomes. We will seek consent from a consultee (which could be the patients' relative, friend or carer).

We will seek Research Ethics Committee approval for the study and will complete all necessary research permissions through the Health Research Authority, including the confidential Advisory Group (CAG). In addition, information governance approvals will be needed to carry out data linkage and retrieval of outcomes for analysis, from SAIL in Wales (Information Governance Research Panel, IGRP); and NHS Digital in England (via its Data Access Request Service DARS). Although these permissions processes can be time consuming, we have strong experience and track records across the team of having successfully completed these processes and retrieved data to deliver funded studies including SAFER 2 (HTA) [48] and PRISMATIC (HS&DR) [56].

Consent

It is acknowledged that it is not ethically appropriate to consent patients who are in pain or shock to research within the context of a medical emergency [57]. We have experience of carrying out randomised trials in emergency care through the SAFER programme [48, 58] and have successfully gained ethical, research and information governance approvals to inform people of their inclusion in research following their attendance by emergency ambulance within ten working days. Patients attended by paramedics for suspected hip fracture are at high risk of being in extreme pain distress. They may have been lying on the floor for some time – up to four hours in RAPID and most had no recollection of their treatment when asked at follow up [59]. In such circumstances, it is not appropriate to consent patients to research [48], although, following standard clinical practice, patients will be consented to treatment in each arm of the trial for follow-up. Following the approach used successfully in the RAPID feasibility trail, we propose that consent to questionnaire follow up in the trial is taken by a trained NHS researcher within approximately ten working days of the patient's injury. This is most likely to occur in hospital, but will be taken in the community for patients recruited to the trial but then either discharged relatively

quickly from or not admitted to hospital. Importantly, the consent taken at this point will be for questionnaire follow up only.

We will include all participants in follow up of routine data, using anonymised linked data, unless they specifically dissent from this. This will be explained on our participant information leaflet, and opportunities to consent to questionnaire follow up and to dissent from routine follow up will be shared by the NHS researcher. The NHS research officer will address any questions that the patient has about this. Participants will be advised that they can withdraw from the trial at any point without this decision affecting their care. As some people will not be seen by the researcher (e.g. because they are too unwell or are unavailable) a wider opportunity to dissent from anonymised data follow up will be made available and publicised on participating Trust websites.

For patients with cognitive impairment, assent to their participation in the trial will be sought from relatives or carers.

Patients (or relatives/carers) will be given a copy of the written consent (or assent), and advised to keep it with the information sheet, so that they can refer back to these documents at any point during the trial.

Mortality is an important outcome of this trial and to exclude patients who die before consent can be requested would mean that the results are not valid for the population. If a patient has been identified as eligible for the trial and randomly allocated to a trial arm, but dies before the NHS researcher approaches them for consent, it is likely to be distressing for a personal consultee to be approached regarding the research use of routinely collected healthcare data. Under these circumstances, we propose that they are included in the anonymised data.

We have included PPI representatives in discussions about this approach, successfully used in our RAPID feasibility trial, and it is their view that it minimises intrusion and possible distress to patients and carers, yet allowing the opportunity for informed involvement in patient follow up via patient reported outcomes for those patients who were able to complete the questionnaires. All patient-facing documents will be prepared in careful consultation with the PPI members of the research team.

Confidentiality

Personal information will be required to monitor for SAEs and to send the participants questionnaires. They will be seen by NHS researchers only. These will be held 1) on paper CRFs – physically stored in locked files at each site, and 2) electronically – stored on password protected files. The storage of these files after the trial will follow the archiving policies of Swansea University, and each of the five participating ambulance service NHS Trusts.

Declaration of Interests

Helen Snooks is a member of the Health Technology Assessment Editorial Board and senior scientific advisor to the Health Services and Delivery Research programme.
Steve Goodacre is Chair of the Health Technology Assessment Clinical Trials funding Board.

Access to Data

Any requests for the full trial dataset following the trial will be considered by our statistician, Alan Watkins, in line with SAIL Standard operating Procedures for data privacy/sharing.

Ancillary and Post-trial Care

As this trial involves an acute intervention within ambulance services, with participant care immediately handed over to a hospital, we do not envisage participants requiring ancillary or post-trial care. Patients that are enrolled into the study are covered by indemnity for negligent harm through the standard NHS Indemnity arrangements. Swansea University has insurance to cover for non-negligent harm associated with the protocol. This will include cover for additional health care, compensation or damages whether awarded voluntarily by the Sponsor, or by claims

pursued through the courts. Incidences judged to arise from negligence (including those due to major protocol violations) will not be covered by study insurance policies.

Dissemination Policy

Our dissemination approach will seek to maximise stakeholder interest and understanding of the study and its outputs and maximise the impact of the findings on ambulance service policy, processes, practice and patients. It will build on the team's profile and reputation with previous studies focused on improving the quality of prehospital care. At an early stage we will develop a communications, publications and dissemination plan including the assessment of stakeholder needs and communications activities and milestones. The plan will include engagement with patient and professional groups, NHS managers, commissioners and policy makers. We will produce lay summaries with our PPI reps where appropriate. Key audience groups for dissemination will include policy-makers on emergency care, care-commissioning bodies and ambulance service providers, emergency-care practitioners and the general public. We will ensure that we maintain engagement with practitioners during dissemination activities.
Our communications, publications and dissemination plan will also contain media engagement, to include written press coverage, online media, and social networking, with the support of the dedicated marketing team in Swansea University Medical School. We will use our strong links with ambulance services directly and through national bodies (National Ambulance Research Steering Group, National Ambulance Services Clinical Quality Group, Association of Ambulance Chief Executives and National Ambulance Services Medical Directors) and other health service providers to develop plans for dissemination of findings through trade/professional publications and networks. We will work with our PPI contributors in the development of dissemination plans. Given the implications for practice, policy and research we will disseminate findings through the annual 999 EMS Research Forum Conference http://www.999emsresearch.co.uk/en/, which is hosted each year by a UK ambulance service and is administered by Swansea University PRIME Research Centre for Unscheduled Care and brings together academics and practitioners. In addition to a full final study report, we will produce a summary version to be disseminated through the PRIME network (http://www.primecentre.wales). We will also present findings at other appropriate national and international events, such as the Health Services Research Network annual conference, the International Forum for Quality in Healthcare and the European Society for Emergency Medicine.

Outputs of the research will include:

1) A final comprehensive research report detailing all the work undertaken together with supporting technical appendices, abstract and executive summary. The plain English executive summary will focus on results/findings and be suitable for use separately from the report as a briefing for NHS managers, emergency care practitioners and the general public.
2) Interim reports at intervals agreed with the HTA.
3) A set of PowerPoint slides which present the main findings from the research for use by the research team or others in disseminating research findings to the NHS and other stakeholders.
4) Papers for academic peer reviewed journals such as the Annals of Emergency Medicine, Emergency Medical Journal and BMC Emergency Medicine to ensure the research forms part of the scientific literature and is available to other researchers. We support an open access model of research dissemination.
5) Articles for professional journals which are read by the NHS management community and which will be helpful in raising wider awareness of the research findings e.g. Ambulance UK, Health Service Journal.
6) Seminars, workshops, conferences at regional, national and international level or other interactive events at which the research team will present and discuss the research and its findings with NHS managers.

7) User-friendly materials for service managers and commissioners/ policy makers using infographics to maximise accessibility and reach.

The study's impact will be shown if and when clinical guidelines either recommend or reject the use of FICB in routine practice in the NHS.

Study timetable

Dec 2020 – Jan 2021	2 months trial manager funding only to begin applications to HRA (REC, CAG, site R&D), IGRP (SAIL) and DAR (NHS Digital)
Feb – May 2021	4 months study set up • Complete ethics, research and governance permissions • Arrange contracts and collaboration agreements • Recruitment of trial site staff (administrator and researcher) • Advertise to and recruit paramedics • Prepare randomisation schedule and scratchcards
June – September 2021	4 months training paramedics • Give all instructions and relevant links for e-learning to paramedics • Give all written material to paramedics • Arrange rooms for classroom sessions and provide them • Arrange mutually convenient dates for anaesthetists and paramedics to attend in hospital training in pairs Site researchers will issue scratchcard sets to paramedics when they have completed all training elements, passed written assessment of trial methods and been signed off as competent to give FICB by the training anaesthetist.
October 2021 – March 2022	• 6 month pilot phase of recruitment • Review of pilot data against preset criteria
April 2022 – September 2023	• Further 18 months patient recruitment, to complete a total of 24 months • Refresher training to be completed as required
November 2021 – January 2024	1 and 4 months follow up
February – July 2024	6 months to allow for lag in linked data (no cost)
August 2024 – January 2025	• Analysis and write up • Dissemination of study results

Patient and Public Involvement

We have actively involved patients and public members in developing this project proposal and will continue to do so in our proposed research. Our public contributor, SJ, has been an integral member of our co-applicant team and has undertaken a valuable role consulting wider groups of public and patient members to help us decide what outcome measures to include in this study. She has also been involved in all the other discussions, decisions and review tasks, which have been necessary while developing and agreeing this research protocol. We have drawn on her patient expertise when considering how to make our research as ethical, safe, relevant and efficient as possible for patients who will take part in our study: for example, reviewing treatment procedures, patient consent processes and participant incentives during data collection. We will recruit a second public contributor to join her on the TMG.

In order to improve trial implementation at sites, ensuring that patient and public voice is ubiquitous, we will recruit two public contributors to each of the five local implementation teams (10 in total). These local members will be recruited from existing groups where possible (for example the SUPER group for the Welsh Ambulance Service site). This approach was successfully utilised in the SAFER 2 trial [60].

We will recruit two public contributors to both the TSC and DMC to provide trial oversight (four in total). To enable our public contributors to be effectively involved throughout the research, we will use the UK Standards for Public Involvement [61] to guide us. We have named and budgeted co-applicant BAE as their contact person. She will provide support and identify training needs.

Disclaimer

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