University Hospitals Plymouth NHS Trust

The SToICAL Study

The **S**oft **T**issue **I**njection of **C**orticosteroid **A**nd **L**ocal anaesthetic Study – A single site, non-inferiority randomised control trial evaluating pain after soft tissue corticosteroid injections with and without local anaesthetic

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Sponsor

University Hospitals Plymouth NHS Trust is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Manager at:

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Funder

This study will be funded by available Departmental research funds. Depending on the study cost analysis review further external funds may have to be sought.

This protocol describes the study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS UK Policy Framework for Health and Social Care Research (2017). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CRF	Case Report Form
CT	Clinical Trials
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
NHS	National Health Service
NRES	National Research Ethics Service
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
SmPC/SPC	Summary of Products Characteristics
SOP	Standard Operating Procedure
TMF	Trial Master File
TSG	Trials Steering Group

KEYWORDS

Corticosteroid
Local anaesthetic
Trigger finger
De Quervains tenosynovitis
Carpal tunnel syndrome

University Hospitals Plymouth NHS Trust

STUDY SUMMARY

TITLE	The STolCAL Study: The **S**oft **T**issue **I**njection of **C**orticosteroid **A**nd **L**ocal anaesthetic Study – A single site non-inferiority randomised control trial evaluating pain after soft tissue corticosteroid injections with and without local anaesthetic
DESIGN	A single site, patient and assessor blinded, non-inferiority randomised control trial of patients with a clinical diagnosis of trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome, treated with a corticosteroid injection co-administered with or without local anaesthetic.
AIMS	To determine whether pain experienced during the 24 hours after a corticosteroid injection to the hand and wrist is no worse than (not inferior to) the pain experienced after a corticosteroid and local anaesthetic injection.
OUTCOME MEASURES	The primary objective; Investigate whether there is a difference in pain VAS scores at 1-hour after a corticosteroid injection for trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome co-administered with or without local anaesthetic. The secondary objectives; i) Investigate whether there is a difference in pain VAS scores during the 24-hours after a corticosteroid injection for trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome co-administered with or without local anaesthetic. ii) Investigate whether there is a difference in the pain VAS scores at the time of the corticosteroid injection for trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome co-administered with or without local anaesthetic. iii) Investigate the difference in the additional analgesia required and in the functional use of the hand during the first 3 hours following a corticosteroid injection for trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome co-administered with or without local anaesthetic. These outcomes will be determined by assessing patients' pain using a 100mm VAS score before and at time of the injection, and at 5-minutes, 1-hour, 2-hours, 3-hours and 24-hours after the injection. This will be supplemented by questions to determine whether additional analgesia was required and if there was any effect on hand function following the injection. No subgroup analysis will be performed.
POPULATION	Patients attending elective hand and wrist outpatient clinics at the University Hospitals Plymouth NHS Trust with a clinical diagnosis of trigger finger, de Quervains and carpal tunnel syndrome.
ELIGIBILITY	All patients over the age 18 years old with a clinical diagnosis of trigger finger, de Quervains tenosynvitis or carpal tunnel syndrome and who are able to give written informed consent for treatment will be included. Patients will be excluded if they have had previous surgery or corticosteroid injection for the condition being treated at the site considered for injection. A previous corticosteroid injection elsewhere in the hand does not exclude a patient from the trial. Those who are pregnant, breast-feeding or who have a history of hypersensitivity to corticosteroid or local anaesthetic will be excluded.
DURATION	The study will run for a 12-month period or until 100 patients have been recruited to the trial.

1. INTRODUCTION

1.1 BACKGROUND

Corticosteroid injections are used in the treatment of a variety of hand and wrist conditions. They have local anti-inflammatory effects from blocking cytokine production involved in the inflammation process[1]. The injections can be administered intra or extra-articularly, with or without image guidance and with or without local anaesthetic. The co-administration of a local anaesthetic and corticosteroid aims to reduce pain soon after the injection. However no studies have directly compared this with using corticosteroid alone, to determine whether there is a difference in patients pain.

Conditions:
Trigger finger, de Quervains tenosynovitis and carpal tunnel syndrome are painful conditions of the hand and wrist where corticosteroid injections have a role in their treatment.

Trigger finger is a condition that causes locking on flexion of the involved finger, dysfunction and pain as a result of thickening of the first annular pulley, which affects 2% of the general population[2, 3]. Available treatments are operative (A1 pulley release) and non-operative (corticosteroid injection and splinting). Operative treatment has an effective cure rate of 89-97% with increased costs, longer absence from work, and the possibility of surgical complications[4]. Corticosteroid injection is an effective and safe treatment with cure rates ranging from 60-92%[3].

De Quervains tenosynovitis is a disorder that causes radial sided wrist pain as a result of mechanical impingement of the tendons within the first extensor compartment[5]. The prevalence of de Quervains tenosynovitis in the United Kingdom is 0.5% in men and 1.3% in women[6]. Available treatments are operative (slitting or removing a strip of the tendon sheath) and non-operative (corticosteroid injection and splinting). Operative treatment has an effect cure rate of 91%, but is more invasive and associated with higher costs and the possibility of surgical complications[7]. Corticosteroid injections have cure rate of 83% and is a superior treatment compared to splinting[8].

Carpal tunnel syndrome causes pain and numbness in a median nerve distribution in the hand from compression of the nerve within the carpal tunnel, and affects 3.8% of the general population[9, 10]. Available treatments are operative (Carpal tunnel decompression) and non-operative (corticosteroid injection and wrist splinting). Surgery is preferred in severe cases whereas in mild and moderate case non-surgery treatments are used initially[11].

Administration:
Corticosteroid injections administered into soft tissue for these conditions can be performed under ultrasound guidance or by using anatomical landmarks. Landmark guided injections can be performed at the time of consultation within the outpatient clinic without additional imaging. Ultrasound guided injections are performed by the radiology department with variable on-the-day availability. Often a separate outpatient appointment is required to deliver this treatment. The accuracy and effectiveness of both methods of delivery have been studied.

A cadaveric study showed no statistical difference in the accuracy between ultrasound and landmark guided injections for de Quervains tenosynovitis or carpal tunnel syndrome. The incidence of success without ultrasound guidance was 95% and 100% for de Quervains tenosynovitis and carpal tunnel syndrome respectively; injections for trigger finger were not included[12]. Despite both ultrasound and landmark guided injections being effective in reducing symptoms and improving hand function in carpal tunnel syndrome, ultrasound guided injections have shown superior clinical outcomes[13,14].

Although no clinical study directly compared ultrasound versus landmark guided corticosteroid injections for de Quervains tenosynovitis, there is evidence suggesting that ultrasound guidance has a slightly

better clinical outcome. A pooled quantitative literature evaluation of landmark-guided injections showed a complete resolution of symptoms in 83% of patients, compared to 92% in a study using ultrasound guidance[8,15]. A prospective randomised trial showed no superior clinical benefit in administering corticosteroid injections for trigger finger with ultrasound guidance, and noted the extra time and effort required[16]. There is also no benefit to injecting the corticosteroid into the tendon sheath versus outside the sheath[17].

Landmark guided corticosteroid injections for trigger finger, de Quervains tenosynovitis and carpal tunnel syndrome are performed routinely in clinical practice across the National Health Service (NHS). Evidence supports the efficacy for landmark guided injections, although in some conditions the use of ultrasound can slightly improve clinical outcomes. However, nowhere considers the additional costs, the delay in treatment and the patient experience benefits of receiving an on-the-day clinic based treatment.

The number of corticosteroid injections given at University Hospitals Plymouth NHS Trust in the elective hand and wrist clinic was determined using clinical codes. 25 patients over a 6-month period were coded to have had a corticosteroid injection. It is likely the coding system is not accurately capturing all corticosteroid injections performed. Anecdotally it is felt that 3-5 corticosteroid injections are performed each week. In light of this, a three week prospective audit was conducted during which 11 corticosteroid injections were performed, which is an average of 3.6 per week.

Corticosteroid injections:
There are a variety of injectable synthetic corticosteroids with different half-lives and variable duration of clinical benefit even between individuals with the same corticosteroid[18]. Triamcinolone (40mg/1ml) is used routinely for soft tissue corticosteroid injections of the hand and wrist at University Hospitals Plymouth NHS Trust by the local Hand and Wrist surgeons.

There are a number of possible adverse effects with corticosteroid injections, which include; local infection, skin atrophy, skin depigmentation, fat necrosis and allergic reactions[19]. It can increase blood glucose level in diabetic patients for up to 5 days, although a study of extra-articular injections in the hand and wrist showed that this was not clinically significant[20]. The National Institute for Clinical Excellence (NICE) recommends that caution be used if the patient is taking oral anti-coagulation[21], but it is not a contra-indication. Another possible adverse effect is a post injection flare, which is a local increase in inflammation that develops within hours and can last 2-3 days[22]. The post injection flare has been described in intra-articular injections to begin after 90 minutes, last for less than 24 hours and be as a result of a crystal-induced synovitis[23]. It may then be 3 to 7 days before the corticosteroid becomes effective[24].

The Cochrane reviews for corticosteroid injection in trigger finger and de Quervains reported no adverse events[2, 5]. A review of over 9000 corticosteroid injections for carpal tunnel syndrome found; severe side effects in <0.1%(tendon rupture, intraneural injection, gangrene), minor persistent local effects in 2%, (subcutaneous atrophy, depigmentation) and transient effects in 15-20% (pain, bruising, facial flushing)[25].

Local anaesthetic:
Corticosteroids are often mixed with local anaesthetic and co-administered to reduce pain after the injection. 1ml of 1% lidocaine is often mixed with 1ml Triamcinolone (40mg/1ml) as part of routine practice for soft tissue corticosteroid injections in the hand and wrist at University Hospital NHS Trust by the local Hand and Wrist surgeons. The mixing does not create a greater propensity for corticosteroid crystals to aggregate or change size; therefore they are safe to co-administer[26].

Lidocaine is a local anaesthetic with a rapid onset of less than 2 minutes and its effects can last for 1 to 3 hours, and has a maximum dose of 5mg/kg[27]. Lidocaine works by blocking voltage gated sodium channels in neuronal cell membranes preventing the propagation of action potentials. The British

National Formulary advises that local anaesthetic should not be injected into inflamed or infected tissues[28].

An injection containing lidocaine can be painful because of the acidity of the solution, which can be neutralised with sodium bicarbonate. However, a randomised control trial failed to demonstrate a statistically significant benefit of sodium bicarbonate in extra-articular corticosteroid injections with local anaesthetic in the hand and wrist[22].

Assessment of pain:
Pain is subjective and multi-dimensional therefore it is difficult to fully evaluate the complete pain experience. The 100mm visual analogue scale (VAS) score is a widely used method for assessing pain. It is generally accepted that a pain VAS score of 30, 70 and 100 indicates the upper boundaries of mild, moderate and severe pain intensity[29].

A reduction in pain score does not directly correlate with an improvement in a patients' experience of that pain. Minimally clinically important difference (MCID) is what minimal change in a pain VAS score would indicate a real change in a patients' pain intensity. A systematic review of 29 studies identified an absolute MCID ranging from 8mm to 40mm and could not conclude a single MCID value because of the variety of different methods used to calculate the MCID. The importance of making a comparison against a patients' baseline pain was recognised[30].

The authors are not aware of any studies that have evaluated the MCID in pain VAS score following soft tissue corticosteroid injection in the hand and wrist. A recent observational study assessed MCID in VAS score in 224 post-operative patients concluded a MCID in pain VAS score of 10mm[31]. Two different papers determine 14mm as the MCID in pain VAS score in treatment of rotator cuff disease and following shoulder arthroplasty[32, 33]. A large prospective multicentre study determined the MCID in pain VAS score in those with knee osteoarthritis to be 19.9mm[34]. This study was reference and a MCID of 20mm used to evaluate patient reported outcomes following arthroplasty surgery[35]. A 20mm MCID has also been used in other studies evaluating post procedural pain[36], one of which was also investigating pain following soft tissue corticosteroid injections in the hand[22]. Therefore, for the purpose of this study a MCID of 20mm will be used.

Non-inferiority studies:
Non-inferiority studies are a one-sided test used to determine if a novel treatment is no worse than the standard treatment. It is designed to show that the novel treatment is no less than a pre-specified un-important amount from the standard intervention. Equivalence studies are a two-sided test used to show a novel treatment is no worse or no better than the standard treatment. It is designed to show that the two treatments do not differ in either direction by more than a pre-specified unimportant amount. This pre-specific unimportant amount is the margin that defines the "zone of indifference" within which the interventions are considered equivalent or non-inferior. Non-inferiority studies are often used in therapeutic trials when a novel treatment offers additional benefits to the standard treatment and the aim is to show that is non-inferior[37,38].

In this instance the standard treatment is considered as a corticosteroid co-administered with local anaesthetic and the novel treatment corticosteroid alone. The hypothesis is that the pain at 1-hour post injection of corticosteroid alone is no worse than (not inferior to) the pain following a corticosteroid injection co-administered with local anaesthetic. The benefits of injecting corticosteroid alone, if the post injection pain was not inferior to co-administering it with local anaesthetic includes; stopping unnecessary administration of medication and reducing treatment time and cost. The zone of indifference has been set at <20mm, which has been determined from a MCID of 20mm a value below which it has been shown that there is no difference in pain experienced by the patient.

1.2 RATIONALE FOR CURRENT STUDY

Study: The SToICAL Study

The authors are not aware that a study exists that assesses pain following soft tissue corticosteroid injections in the hand and wrist, co-administered with and without local anaesthetic. Although, corticosteroids and local anaesthetic are often co-administered no evidence is currently available to support this.

The effects of the local anaesthetic only last for 2-3 hours; therefore it would not provide relief from post-procedure flares nor bridge the time until the corticosteroid becomes effective. Administering local anaesthetic can be painful because of the acidity of the solution and means higher volume injections are given. The use of local anaesthetic may also worsen paraesthesia symptoms or result in paraesthesia in parts of the hand, preventing normal function for the duration of its action.

Adding local anaesthetic increases the cost, time and clinical waste of the treatment. Although, the additional cost per treatment may not be significant when considering the number performed across the National Health Service, the saving may be considerable.

We hypothesise, that the pain experienced at 1-hour after a corticosteroid injection for trigger finger, de Quervains tenosynovitis and carpal tunnel syndrome is no worse than when the corticosteroid is co-administered with local anaesthetic.

1.3 PATIENT AND PUBLIC INVOLVEMENT

This study proposal was discussed with a number of patients within the hand clinic. To collect objective evidence a patient opinion questionnaire was developed.

13 patients completed this questionnaire of which 10 had had previous corticosteroid injections (9 for trigger finger and 1 for carpal tunnel syndrome). 7 were given the injection with local anaesthetic, 1 without local aesthetic and 1 did not know if local anaesthetic was used or not. All 13 patients indicated that they would be able to complete and return the proposed patient assessment form and if asked would agree to be randomised into this study.

When asked about their thoughts about being include in a study like this, patients responded:
“Not a problem”
“I would be willing to help the study”
“Great study as could be wasting money”
“No problem whatsoever”
“I’ll be happy if it can help doctors with patients’ treatment”

When asked what would put them off about being included the majority said “nothing”, however 2 patients who had had injections before were reluctant to have further injections because they were painful and not well tolerated.

2. STUDY OBJECTIVES

The primary objective;
Investigate whether there is a difference in pain VAS scores at 1-hour after a corticosteroid injection for trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome co-administered with or without local anaesthetic.

The secondary objectives;
i) Investigate whether there is a difference in pain VAS scores during the 24-hours after a corticosteroid injection for trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome co-administered with or without local anaesthetic.

ii) Investigate whether there is a difference in the pain VAS scores at the time of the corticosteroid injection for trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome co-administered with or without local anaesthetic.

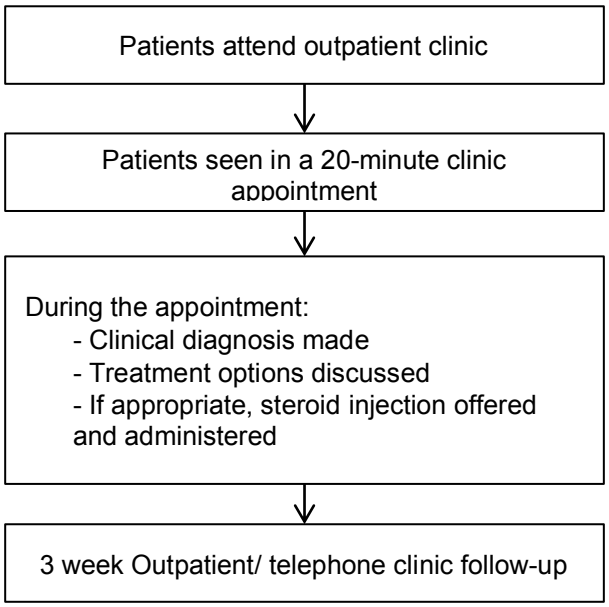
iii) Investigate the difference in the additional analgesia required and in the functional use of the hand during the first 3 hours following a corticosteroid injection for trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome co-administered with or without local anaesthetic.

3. STUDY DESIGN

This is a single site, patient and assessor blinded, non-inferiority randomised control trial where patients will be randomised to receive an injection of corticosteroid alone or an injection of corticosteroid co-administered with local anaesthetic to treat; trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome.

The reviewing physician will identify eligible patients during 20-minute outpatient hand and wrist clinic appointments. Providing that the patient meets the inclusion and exclusion criteria the supernumerary registrar in clinic will explain the study to the patient and provide them with an information leaflet (Appendix 1). Patients considering enrolment will return to the waiting room to read the study information. This allows sufficient time for the patients to go through the information at their own pace and for the clinic to continue to avoid it running behind. The patients can have the duration of the morning clinic (if required) to consider enrolment in the study. After the patients have read the study information they will return to clinic as soon as they are ready and be seen by the registrar a separate clinic room. There will be no pressure to participate and if patients do not want to be included they will still receive treatment within the clinic, as they would do normally.

Normal practice for patients attending outpatient hand and wrist clinic with a clinical diagnosis of trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome:



Once the patient feels well informed and comfortable to participate, consent will be received (Appendix 2) and a patient participation record completed (Appendix 3). A photocopy of the consent form will be given to the patient and another copy kept in the patients' hospital notes. The original consent form will be kept in the site file along with the patients' participation record. The patient participation record contains a patient participation number, which is the only link between the patient and the treatment

delivered. The supernumerary registrar uses a computerised randomisation system to randomise the patient into one of the two treatment arms, whilst the patient completes the pre-injection validated pain VAS score on the patient assessment record (Appendix 4).

Patients will be randomised using the simple randomisation service provided by Sealed Envelope Ltd. This is an online service that provides random permuted block randomisation, ensuring participants are balanced between the control and treatment group. The physician will use a unique URL and password to randomise patients in A (treatment) or B (control) group.

Patients will receive injections containing one of the two following solutions, delivered under landmarks guidance to treat either; trigger finger, de Quervains tenosynovitis or carpal tunnel. Both combinations are used as part of routine practice for soft tissue corticosteroid injections in the hand and wrist at University Hospital NHS Trust by the local Hand and Wrist surgeons:

A. 1ml of triamcinolone (40mg/1ml)
   or
B. 1ml of triamcinolone (40mg/1ml) + 1ml 1% Lidocaine

The registrar will draw up, prepare the treatment in a separate room so that the patient will remain blinded. Neither treatment can be distinguished from one another by their appearance alone.

During the clinic appointment the patient will complete a pain VAS score prior to the injection, for pain experience at the time of the injection and at 5 minutes post injection on the patient assessment record. The pain VAS score of the pain experience during the corticosteroid steroid will be recorded immediately after the procedure. The patient then takes the patient assessment record home to complete further pain VAS scores at; 1-hour, 2-hour, 3-hour and 24-hours following the injection. The timings at which these scores must be recorded will be clearly documented on the patient assessment record by the physician before leaving clinic to help remind the patient. There are three further questions, on the same form; that the patient will be required to answer at 3-hours post injection (Appendix 4).

During the first 3-hours after your steroid injection:

1. Did you take any additional painkillers because of pain at the injection site?
   YES ☐ Medication: _____
   Time taken: _____
   NO ☐ (go to next question)

2. Did you have any reduction in hand function, below normal, as a result of the injection?
   YES ☐, please describe your reduction in function:
   _____
   _____
   NO ☐

3. Did you experience any new numbness in your hand, as a result of the injection?
   YES ☐

   NO ☐

After the final pain VAS score at 24-hours the patient will receive a follow-up call by the registrar to ensure the assessment form has been completed, to answer any questions and remind the patient to

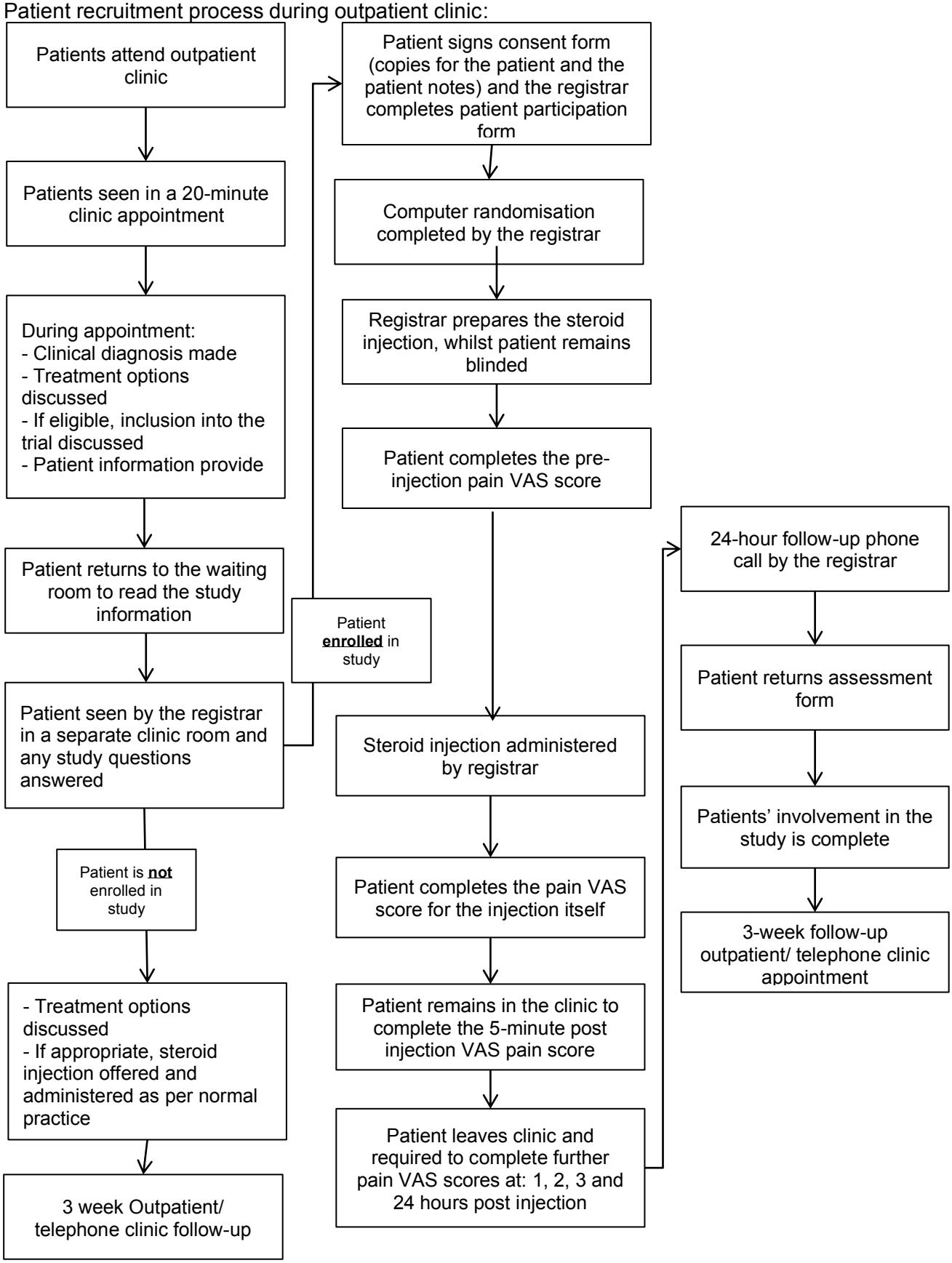
return the form using the prepaid envelope provided. After the form is posted the patients participation in the study will be complete.

The routine dictated clinic letter completed by the physician will outline the patients diagnosis, inclusion into the trial, and an overview of the trial and the consent process, but will not specify which treatment was delivered. A copy of this letter is kept in the patients' notes and a copy is sent to the GP.

The patient participation record and a copy of the consent form will be kept in the site file and stored in a locked filling cabinet in Mr Gozzard's Office, Level 11, Derriford Hospital.

Returned patient assessment records will be collected by the departmental secretary, held within the site file and remain sealed until the end of recruitment. Once the recruitment phase is completed the patient assessment records will be open and the pain VAS scores will be measured, recorded on an excel spread sheet then statistically analysed by a blinded assessor (Mr M Jones - A member of the study management team, but directly not involved in patient recruitment). The same individual, who will not be involved in patient recruitment, will take all the measurements. Measurements will be taken using a standard 20cm ruler with 1mm increments and recorded to the nearest. Incomplete patient assessment records will be included on an intention to treat basis. A summary of the investigations, treatment and assessment can be found in Appendix 5. A planned time for the SToICAL study is outline in a Chart (Appendix 6)

Patient recruitment process during outpatient clinic:



3.1 STUDY OUTCOME MEASURES

Patients pain will be measured using a 100mm pain VAS score which they will complete on a paper form; before the injection, at the time of injection, then 5-minutes, 1-hour, 2-hours, 3-hours and 24-hours after the injection. Patients will remain active in the study until the final VAS score is completed and the form is returned.

Assessment of additional analgesia required and any reduction in hand function will be determined by the patients answers to the following three question, which are completed 3-hours after the injection (Appendix 5).

During the first 3-hours after your steroid injection:

1. Did you take any additional painkillers because of pain at the injection site?
   YES ☐ Medication: _____
   Time taken: _____
   NO ☐ (go to next question)

2. Did you have any reduction in hand function, below normal, as a result of the injection?
   YES ☐, please describe your reduction in function:
   _____
   _____
   NO ☐

3. Did you experience any new numbness in your hand, as a result of the injection?
   YES ☐

   NO ☐

The study will end once 100 patients have been recruited, which includes 82 patients to achieve 95% power, plus 20% to account for potential dropouts. With an average of 3.6 corticosteroid injections given every week and an estimated 60% capture rate, full recruitment should be achievable within 12 months.

4. PARTICIPANT ENTRY

4.1 RECRUITMENT

The reviewing physician will approach potentially eligible patients for the study during a clinic they are routinely attending after determining whether they meet the inclusion /exclusion criteria. All patients will be spoken to in person during their clinic appointment. Potential participants will have the duration of the morning clinic to decide whether or not to participate in the study. It is standard practice to offer and deliver a corticosteroid injection within a 20 minutes clinic appointment, without pre-warning that this may be appropriate or available within clinic. Patients rarely need additional time to decide if they would like this on the day treatment.

A verbal explanation of the trial and why the patient has been invited to participate will be given, together with a Participant Information Sheet (Appendix 2) and a copy of the Patient Consent Form (Appendix 3). The patient will also be given the contact details of the Hand and Wrist Registrar/ Mr Gozzard should they wish to seek further information about the study.

Recruitment will continue until 100 patients have been randomised and received the study intervention.

4.2 PRE-REGISTRATION EVALUATIONS

The patient participation record (Appendix 4) must be completed prior to inclusion; however there are no further pre-registration tests required for the patient to be included.

4.3 INCLUSION CRITERIA

- Male or female ages >/= 18 years
- A clinical diagnosis of trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome made by a consultant physician.
    - Trigger finger: A diagnosis made on a history of triggering together with clinical findings of pain localised to the first annular pulley along with triggering of the affected digit
    - De Quervains tenosynovitis: A diagnosis made on clinical examination findings of pain over the first dorsal compartment, swelling localised to the first dorsal compartment and a positive Finklestein test.
    - Carpal tunnel syndrome: A diagnosis made on a history of intermittent paraesthesia in the radial 3.5 digits, with nocturnal symptoms and subjective sensory impairment and thumb weakness.
- Treatment with corticosteroid injection is recommended by the doctor and agreed by the patient
- Patient is willing and able to give informed consent for participation in the study

4.4 EXCLUSION CRITERIA

- Previous surgery for the condition being treated at the desired location of injection*
- Previous steroid injection for the condition being treated at the desired location of injection*
- Clinical suspicion of local or systematic sepsis or infection
- History of hypersensitivity to the corticosteroid or local anaesthetic
- Pregnant or breast-feeding females
- Unable to understand and complete self-report questionnaires written in English

*Previous surgery or a corticosteroid injection elsewhere in the hand or wrist does not exclude the patient from the trial

4.5 WITHDRAWAL CRITERIA

Patients are able to with draw from the study at any stage without prejudice.

5. ADVERSE EVENTS

5.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

	All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.2.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.2.2 Serious AEs

"All SAEs / SUSARs occurring from the time of written informed consent until 24 hours post cessation of trial treatment must be recorded on the SAE Form and e-mailed to the Sponsor within 24 hours of the research staff becoming aware of the event. Once all resulting queries have been resolved, the Sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

For each SAEs / SUSARs the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached."

5.2.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)
"All SAEs assigned by the PI or delegate (or following central review by the CI and sponsor) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The Sponsor will inform the MHRA, the REC and the Sponsor of SUSARs within the required expedited reporting timescales."

5.2.4 Notification of deaths
Only deaths that are assessed to be caused by the study medications (Triamcinolone and Lidocaine) will be reported to the sponsor. This report will be immediate.

5.2.5 Pregnancy reporting
Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE.

5.2.6 Overdose
Any overdoses of the study medication will be reported to the CI immediately and will recorded as protocol non-compliance and as an AR/SAR if an untoward reaction is observed.

5.2.7 Reporting urgent safety measures
If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

Please refer to the following website for details on clinical trials safety reporting: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Clinicaltrials/Safetyreporting-SUSARSandASRs/index.htm

5.3 RESPONSIBILITIES

5.3.1 Principal Investigator (PI):
Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and expectedness using the Reference Safety Information approved for the trial.
2. Using medical judgement in assigning seriousness and causality and providing an opinion on expectedness using the Reference Safety Information approved for the trial.
3. Ensuring that all SAEs and SARs (including SUSARs) are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon

as available. Ensuring that SAEs and SARs (including SUSARs) are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.

4. Ensuring that AEs and ARs are recorded and reported to the Sponsor in line with the requirements of the protocol.

5.3.2 Chief Investigator (CI) or delegate:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning seriousness, causality and expectedness of SAEs where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning expectedness.
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

5.3.3 Sponsor:

1. Acknowledgement of reported SAEs, SARs and SUSARs according to the trial protocol.
2. Expedited reporting of SUSARs and Urgent Safety Measures to the Competent Authority (MHRA in UK) and REC within required timelines.
3. The unblinding of a participant for the purpose of expedited SUSAR reporting.
4. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
5. Preparing standard tables and other relevant information for annual reports in collaboration with the CI and ensuring timely submission to the MHRA and REC.

6. ASSESSMENT AND FOLLOW-UP

The end of the trial will be when the patient has completed all pain VAS scores for the documented time points (pre-injection, time of injection, 5-minutes after the injection, 1-hour, 2-hour, 3-hour and 24-hour post injection), answered the three additional questions and returned the form by post.

7. STATISTICS AND DATA ANALYSIS

7.1 DESCRIPTION OF STATISTICAL METHODS

The primary objective;
Investigate whether there is a difference in pain VAS scores at 1-hour after a corticosteroid injection for trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome administered with or without local anaesthetic.

Primary outcome measure of primary objective:
1a) A analysis of the mean change in pain VAC score between 1-hour post injection and baseline pre-injection will be performed. The primary intention will be the use of parametric tests

(Unpaired Students T-test) dependent upon the assessment of score distribution (skewness and kurtosis). Non-parametric testing will be employed if the mean distribution fails tests of normality.

Secondary outcome measures of primary objective:
1b) The effect size at 1-hour post injection will be calculated to measure the significance of the difference between the study and control group.

$$\frac{\textit{Mean score at 1-hour in corticosteroid alone group} - \textit{Mean score at 1-hour in corticosteroid and LA group}}{\text{Standard deviation}}$$

The objectives;
i) Additional sensitivity analysis will be conducted to investigate whether there is a difference in pain VAS scores during the 24-hours after a corticosteroid injection for trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome administered with or without local anaesthetic.

Outcome measure: The cumulative pain in the 24-hour period in both groups will be calculated by using the area under the curve. Multilevel linear regression analysis will be conducted to compare 24 hour pain VAS with injection intervention nested in patient condition.

ii) Additional sensitivity analysis will be conducted to investigate whether there is a difference in the pain VAS scores at the time of the corticosteroid injection for trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome administered with or without local anaesthetic.

Outcome measure: the pain VAS scores in each group at the time of the injection. Multilevel linear regression analysis will be conducted to compare pain VAS with injection intervention nested in patient condition.

iii) Investigate the difference in the additional analgesia required and in the functional use of the hand during the first 3 hours following a corticosteroid injection for trigger finger, de Quervains tenosynovitis or carpal tunnel syndrome administered with or without local anaesthetic.

Outcome measure: The percentage of patients requiring additional analgesia or who experienced worsening hand function will be determined from the three questions asked in the patient assessment record. The results will be presented as numbers with additional details given in the patients' response, but no statistical analysis will be performed on these results.

No interim or subgroup analysis will be performed.

7.2 THE NUMBER OF PARTICIPANTS

Minimally clinical important difference of 20mm will be used as the clinically admissible margin of non-inferiority. From previous studies, it is assumed to use a standard deviation of 25mm and with a 95% power calculations have determined a required sample size of 41 per study arm, when including a 20% fall out rate a total sample size of 100 patients will be required[22].

7.3 THE LEVEL OF STATISTICAL SIGNIFICANCE

. All statistical testing was done at the two-sided 5% significance level, and 95% CIs with Stata 14.2.

7.4 RANDOMISATION

Patients will be randomised using the simple randomisation service provided by Sealed Envelope Ltd (https://www.sealedenvelope.com). This is an online service that provides random permuted block randomisation, ensuring participants are balanced between the control and treatment group.

7.5 CRITERIA FOR THE TERMINATION OF THE TRIAL.

Once 100 patients have been recruited and randomised to the trial.

7.6 PROCEDURE FOR ACCOUNTING FOR MISSING, UNUSED, AND SPURIOUS DATA.

A 20% fall out rate has been considered. Participants who have not returned their patient assessment records will not be included in the analysis. Results from partially completed forms will be included for analysis.

7.7 INCLUSION IN ANALYSIS

All participants who have been randomised and have returned the patient assessment record will be included in an intention to treat analysis.

8. ARCHIVING

Archiving will be authorised by the Sponsor following submission of the end of study report. All essential documents will be archived for a minimum of 5 years after completion of trial. Destruction of essential documents will require authorisation from the study Sponsor.

9. REGULATORY ISSUES

9.1 ETHICS APPROVAL

The CI will obtain a positive opinion from a Health Research Authority (HRA) Research Ethics Committee (REC) for the study.

The CI will also require a HRA approval letter and a Capability and Capacity e-mail statement from the local R&D office before accessing data for inclusion into the study.

Any amendments to the study protocol will require review by HRA (and possibly the REC if the amendment is deemed to be substantial) will not be implemented until the HRA grants a favourable opinion for the study (note that amendments will also need to be reviewed and accepted by the NHS R&D department before they can be implemented in practice).

All correspondence with the HRA will be retained in the Trial Master File/Investigator Site File.

An annual progress report (APR) will be submitted to the HRA within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. It is the CI's responsibility to produce the annual reports as required. The CI will also notify the HRA and sponsor of the end of the study. If the study is ended prematurely, the CI will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the CI will submit a final report with the results, including any publications/abstracts, to the HRA. The investigator will ensure that this study is conducted in full conformity with relevant national regulations and with the Department of Health Research Governance

Framework (2005). The research team will also bear in mind the principles of the Declaration of Helsinki when conducting the study.

9.1.1 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA. The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments

9.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

9.3 CONFIDENTIALITY

The trial staff will ensure that the participants' anonymity is maintained. The participants' data will be pseudonymised (i.e. only initials and a study ID number on the CRF and any electronic database will identify participants). All documents will be stored securely and only be accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act 2018. No participants will be individually identified in any subsequent publications relating to this study.

9.4 INDEMNITY

This is an NHS-sponsored research study. If an individual suffers negligent harm as a result of participating in the study, NHS indemnity covers NHS staff and those people responsible for conducting the trial who have honorary contracts with the relevant NHS Trust. In the case of non-negligent harm, the NHS is unable to agree in advance to pay compensation, but an *ex-gratia* payment may be considered in the event of a claim.

9.5 SPONSOR

University Hospital Plymouth NHS Trust will act as the main sponsor for this study. Delegated responsibilities will be assigned to other NHS trusts taking part in this study.

9.6 FUNDING

This study will be funded by available Departmental research funds, held by the Research and Development department on behalf on Miss S Fullilove. Depending on the study cost analysis review further external funds may have to be sought.

9.7 MONITORING

The study will be subject to monitoring by University Hospitals Plymouth NHS Trust under their remit as sponsor to ensure adherence to the UK Policy Framework for Health and Social Care Research (2017). All UHP studies will be initially monitored at 25 days (+/- 7 days) after R&D capability and capacity has been given. The subsequent level of monitoring will be determined by a risk assessment, or on a for cause basis. The study may also be audited / inspected by regulatory bodies to ensure compliance with national regulations.

10. STUDY MANAGEMENT

The study management group will meet monthly to monitor study process, patient recruitment and potential issues, which may arise. These meetings will include the study management group, consultant sectaries and a member of the R&D team. Minutes will be taken and distributed and any members not on site will have to option to teleconference in.

11. PUBLICATION POLICY

It is proposed that the study team will prepare a plain English summary of the study results, which will be sent to the study participants as soon as possible after the end of the study. The final results of the study will be disseminated *via* presentations at appropriate scientific meetings and conferences and publication in appropriate peer-reviewed journals. Mr Matt Jones will be named as first author in any presentation or publications.

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