Study Title: Synthesising a clinical Prognostic Rule for Ankle Injuries in the Emergency Department

Short title: SPRAINED

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There is no conflict of interest to declare.

[redacted]

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SYNOPSIS

Study Title	Synthesising a clinical Prognostic Rule for Ankle INjuries in the Emergency Department	
Short title	SPRAINED	
Study Design	A prognostic model validation study	
Study Participants	Patients with acute ankle sprain at emergency departments or minor injury units	
Planned Sample Size	675 participants	
Planned Study Period	Project 30 months. Participants in observational cohort study for total of 9 months	
	Objectives	**Outcome measures**
Primary	To validate a clinical prognostic tool that helps to detect risk of poor outcome following ankle sprain for patients presenting to Emergency Departments/Minor Injury Units.	A composite measure indicating poor outcome for participants at 9 months, defined as either moderate/severe pain and/or moderate/sever functional difficulty and/or significant lack of confidence in the ankle and/or recurrent sprain.
Secondary	To record recovery of these patients over 9 months in terms of function, health-related quality of life and health service resource use.	Foot and Ankle Outcome Score (FAOS), EuroQuol EQ-5D-3L and health service resource use items.

1. ABBREVIATIONS

CAI	Chronic ankle instability
CAST	Collaborative Ankle Support Trial
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CTRG	Clinical Trials & Research Governance, University of Oxford
ED	Emergency Department
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
MNGT	Modified Nominal Group Technique
NHS	National Health Service
NIHR HTA	National Institute for Health Research Health Technology Assessment programme
NRES	National Research Ethics Service
OCTRU	Oxford Clinical Trials Research Unit
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
PPI	Patient and public Involvement
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SSC	Study Steering Committee
UK	United Kingdom

2. BACKGROUND AND RATIONALE

2.1. Introduction

Ankle sprains are one of the most common musculoskeletal injuries. Up to 1.5 million people a year in the United Kingdom (UK) attend the Emergency Department (ED) with a sprained ankle. The vast majority of sprains are of the lateral (outside) ligaments, and vary from minor stretching (Grade I, mild sprain) to a complete tear (Grade III, complete sprain). The health costs of managing moderate to severe sprains with a tubi-grip support are on average £135 per sprain, although costs of operative treatment and/or physiotherapy are considerably greater. Including work absence the costs are approximately £900 per patient (2005 prices), with an average of 7 days work absence.[1]

Recovery can be protracted particularly for more severe injury. Recent systematic reviews conclude that approximately 30% of people have problems one year after an ankle sprain depending on the outcome measured and perhaps more importantly, the sampling frame.[2 3] One sequel, chronic ankle instability (CAI) is implicated in the development of ankle osteoarthritis, even without an acute osteochondral lesion.[4] Many studies are restrictive in their sampling frame, either to elite athletes and exclude younger and older people. Studies also have variable inception and follow up points which further complicates interpretation. We report an estimate of 30% for poor outcome at 9 months in the Collaborative Ankle Support Trial (CAST) dataset.[1] Studies agree that recovery plateaus around 9 months, and that residual disability after this point is likely to be persistent.[5]

2.2. Usual clinical pathway

Assessment of the injury in the acute phase is challenging, the ankle is often so swollen and painful that it cannot easily be touched. Most patients are advised to rest, elevate, apply ice and compression, and are often issued with crutches. Use of X-ray has been effectively controlled through the Ottawa guidance,[6] with only the most concerning injuries being X-rayed (or equivalent) to exclude fracture. Where clinicians are concerned about the degree of injury, most providers operate a system of review within weeks in a trauma or equivalent injury service. This time frame allows dissolution of some swelling, and greater certainty in ascertainment of injury severity and presence of other significant mechanical derangement.[7] Treatment options at this stage include further watchful waiting, diagnostics, intensive physiotherapy or immobilisation. Surgery may be considered at this stage, although most centres would initiate a test of conservative treatment first.

2.3. Value of a prognostic tool

We propose to develop a prognostic tool and will assess its use in EDs and Minor Injury Units (MIUs) in terms of ability to predict outcome for patients who have had an ankle sprain, and will identify patients likely to experience poor outcome. There are effective treatments for ankle sprain available, and it is generally accepted that early intervention is preferable. There is an opportunity to introduce better prognostic information in these settings which could yield benefit to the NHS and to patients as follows; (1) Increase the certainty that an early ankle review is merited, and avoid unnecessary appointments (2) Allow appropriate targeted treatments and diagnostics to be used earlier in the recovery pathway, and (3) Be re-assured that patients not followed up are on a positive recovery

trajectory. Patient volume is a key issue for sprains. NHS cost savings will accrue if treatments are more efficiently targeted.

Any prognostic tool document to be used in ED/MIU needs to be simple to complete. Ideally a tool which requires a once only administration is preferable, although there are several possibilities which we will explore in the development stage using both the dataset from the Collaborative Ankle Support Trial (CAST) and feedback from a consensus group meeting involving both clinicians and patients. The issues that we will explore during development will be variable selection, timing and method (self-report versus clinical examination).

2.4. Requirements of a prognostic tool

To be considered useful, a prediction tool should be clinically meaningful, accurate (well calibrated with good discrimination) and generalizable (have been externally validated). Many prognostic tools are developed using datasets that are too small, are not sufficiently generalizable, have questionable methodological quality (in particular no internal or external validation), and use inadequate statistical methods (e.g. R^2 from multivariate regression).

3. OBJECTIVES AND OUTCOME MEASURES

The aim is to validate a prognostic tool for use in EDs/MIUs for patients with acute ankle sprain in order to identify those in whom recovery may be substantially prolonged or incomplete and additional investigation or treatment is indicated. Specifically we will externally validate and optimise the developed tool by recruiting a new cohort of 675 patients from a representative group of NHS EDs and MIUs. Before patient recruitment begins the tool will have been developed and internally validated using the CAST data set and then optimised and formatted using findings from a systematic review and consensus process involving clinician and patient perspectives (see Appendix C).

Objectives	Measures	Time point(s) of evaluation of outcome measures
Primary Objective To validate a clinical prognostic tool that helps to detect risk of poor outcome following ankle sprain for patients presenting to Emergency Departments/Minor Injury Units. **Secondary Objective** To record recovery of these patients over 9 months in terms of function, health-related quality of life and health service resource use.	1 Baseline Clinical Dataset This includes demographic and standard clinical information about the ankle and questions that form the SPRAINED Study Prognostic Tool (clinician and/or patient completed). 2 Follow-up A. Validated Foot and Ankle Outcome Score B. Validated health related quality of life (EuroQuol EQ-5D-3L) C. Health resource use D. Question on re-injury A composite primary outcome measure will be defined, indicating poor outcome for participants at 9 months (defined as either: 1) moderate/severe pain and/or 2) moderate/severe functional difficulty and/or 3) significant lack of confidence in the ankle and/or 4) recurrent sprain).	At initial ED/MIU presentation and up to 4 weeks after study registration. At 4 and 9 months after study registration

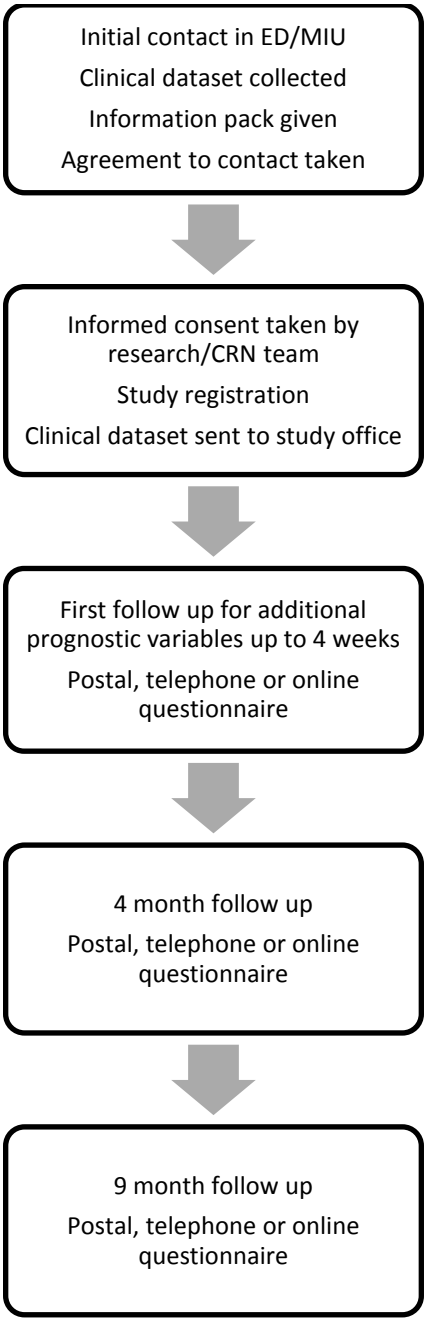
4. STUDY DESIGN

The SPRAINED study has three stages, culminating in an observational validation cohort study. For details of Stages 1 and 2 (model development, systematic review and expert consensus process), please see Appendix C.

In Stage 3 the SPRAINED study will recruit 675 participants across a minimum of 5 EDs and MIUs. This stage will externally validate the prognostic tool developed by the research team in Stages 1 and 2. We cannot be completely certain how the cohort study will run until the results of Stages 1 and 2 are synthesised. Currently we have assumed that the tool will be used at initial ED attendance and once more, up to 4 weeks after study registration. Depending on the final format, the patient or ED clinicians

will be asked to complete the SPRAINED study prognostic tool. The results of the tool would be computed after final follow up. At 4 weeks prognostic and other relevant information will be collected either online, or via telephone/post. Follow up data will be collected from participants at 4 and 9 months via telephone or postal questionnaire and will include capture of severe and persistent symptoms, the validated Foot and Ankle Outcome Score,[8] health service resource use and health related quality of life (EuroQuol EQ-5D-3L)[9].

Figure 1 - Flowchart of Stage 3 cohort study



5. PARTICIPANT IDENTIFICATION

5.1. Study Participants

Patients with an acute (<7days) ankle sprain of any severity aged 16 years or over presenting to participating EDs/MIUs.

This is a cohort study, participants are not randomised and do not receive medical intervention other than standard care.

5.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study
- Male or Female, aged 16 years or above
- Diagnosed with acute ankle sprain (≤ 7 days old)

5.3. Exclusion Criteria

- Ankle fracture (excluding flake fracture ≤ 2mm)
- Other recent (≤ 3 months) lower limb fracture

6. STUDY PROCEDURES

6.1. Recruitment

A minimum of 5 NHS EDs and MIUs will participate to recruit 675 participants. Each site will recruit for approximately 10 months, with a target recruitment rate of approximately 15 patients per month, per site.

The lead site is Oxford University Hospital NHS Trust.

The initial approach will be made by a member of the ED/MIU clinical team. All potentially eligible patients will be given an oral explanation of the study along with a Patient Information Sheet in the department. Posters will be displayed in all participating departments to inform participants the study is taking place.

6.2. Informed Consent

The informed consent process will be carried out by a qualified health care professional with delegated authority from the Principal Investigator (PI). We anticipate in most sites this will be a research nurse/Allied Health Professional (AHP) who will be a part of the local Clinical Research Network team. Prior to consent to participate in the study, the patient will be asked by a member of the local clinical team for permission to allow the local research team to speak to them, either in person or by telephone, to take forward the informed consent process.

In a busy ED/MIU it is possible participants will be discharged quickly and the use of telephone consent will therefore aid the recruitment process.

Formal consent to participate will be either in person or by post or by telephone. Before any data is provided to the study team the participant will either personally sign and date the latest approved version of the Informed Consent form (ICF), or consent will be recorded by a member of the local team on an Oral Consent Form during the informed consent telephone call.

Participants will be consenting to allow the study to use the clinical dataset collected in the ED attendance and up to 4 weeks following study registration (SPRAINED study prognostic tool and any additional important information), as well as follow up questionnaires at 4 and 9 months which map the recovery trajectory and final recovery status at 9 months. A questionnaire at 4 months will serve as reminder of the study, and as loss to follow up is likely to become larger over time, will ensure that we have responses on as many participants as possible.

Written and verbal versions of the Participant Information Leaflet (PIL) and ICF will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will have the opportunity to question the clinical/research team, and may wish to consult their GP or other independent parties to decide whether they will participate in the study. Written informed consent will be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. Oral informed consent will be obtained by means of the dated signature of the local team member taking consent over the telephone. The person who obtained the consent will be suitably qualified and experienced, and have been authorised to do so by the PI.

A copy of the completed written or oral ICF will be retained by the participants (or posted to the participant in the case of oral consent). One copy will be sent to the study coordinating team in Oxford. The original signed Consent Form will be retained in the medical notes, and a copy held in the Investigator Site File (ISF). Holding a copy in the coordinating office will facilitate central monitoring, consent forms will be held in a secure location separately from any study data.

The PIL will outline that the participants name and contact details (including mobile, phone and email), will be collected to facilitate follow up and full data collection. A copy will sent to the study coordinating team in Oxford. These details may be used by the study team to check contact details using the Health and Social Care Information Centre and other central UK NHS bodies, and to provide other basic study-related information that may be needed for follow up.

The ICF will also ask for permission to allow access to participant data by responsible members of the University of Oxford or the NHS Trust for monitoring and/or audit of the study to ensure we are complying with regulations

Permission will be obtained to inform the participants GP of study participation.

A minimum, anonymised data set on people declining (age, gender and severity of sprain) will be collected for the purposes of estimating generalizability of the population recruited.

Some participants will also be given the option to opt in to the use of Dynamic Consent – an electronic tool that will allow participants to engage with the study team online and receive updates on how the study is progressing. The option to use Dynamic Consent will be introduced in the later stages of the recruitment phase, to allow participating centres to fully establish their recruitment systems before adding an additional element to the consent process.

Participants will be consented in the same manner as at the start of the study, but in addition will be asked if they would like to be able to engage with the study online. If they agree, within a week of joining the project they will be sent an email with details of how to access their secure electronic personal profile, which they will access with a username and password. Through this profile they will be able to review their consent choices, and be able to change their preferences as the study progresses. The website will provide a channel of communication between the research team and the study participants to enable the team to send reminders that participants should expect to receive the follow up questionnaires, which we anticipate will help to improve the completion and return rates as the study progresses, while enabling participants to clearly follow their progression through the study and to receive updates on how it is going. Because the study is observational we will not be providing any information that might alter participants' behaviour during their recovery period, and whether participants choose to engage via Dynamic Consent or not is not anticipated to have any influence on the central study or its scientific validity. The purpose of the use of Dynamic Consent is to see whether it improves response rates to the questionnaires – which will be compared between participants that do not sign up to Dynamic Consent (including those that are not offered it as an option in the early stages of recruitment) and those that do. It will not necessarily replace the approved consent procedure, if we encounter substantial site difficulties (for example, the uptake into the study, the amount of time incurred with the new systems are too cumbersome) then the original, approved strategy will be used.

If participants are willing to trial the Dynamic Consent website as part of their research study experience, we will offer the opportunity for them to provide comments on this experience once the SPRAINED study has finished.

6.3. Screening and Eligibility Assessment

Patients will be screened by the ED/MIU clinicians on admission to departments. This may happen in triage or subsequent assessment. The clinician will administer the study Clinical Dataset Form (and complete the SPRAINED study prognostic tool questions), and record responses and findings from their clinical examination. We anticipate that completion of the form will fall into the scope of any practitioner who is capable of taking a history and performing a simple ankle examination. In standard practice this would be nursing, medical, surgical or physiotherapy staff with experience or training in basic orthopaedic and injury management. The short Clinical Dataset Form serves three purposes (1) collection of routine core clinical data set in a tick box format, (2) A tick box to ensure that clinicians have provided potential participants with the trial information pack and a brief explanation of the trial, and (3) A tick box to record whether the patient has given permission for a member of the research team make contact to discuss the study further and complete the informed consent process.

One copy of the Clinical Dataset Form will be filed to the medical notes as a treatment record and a second copy, where agreement is given, is passed to the local research team. The team member will contact the patient and continue the informed consent process. Only when consent has been obtained is the clinical dataset sent to the central study office. The clinical dataset of patients who do not agree to the study will remain at the site in medical notes. These will provide ED attendance statistics against the number of people being approached. Audits will be performed periodically by the local team to inform generalizability of the recruited population.

6.4. Baseline Assessments

Baseline data will be collected on the clinician-completed Clinical Dataset Form which includes:

1. Demographics (name, age, contact details)
2. Patient history
3. Clinical examination
4. Clinical Investigation
5. Clinical Management
6. Clinical Diagnosis
7. Prognostic tool questions
8. Agreement for research team to contact patient

Participant contact details will be collected at baseline to facilitate study follow up. This will include full name, address, NHS number, mobile and/or telephone number, email address and a preferred time to be contacted. Reasons for declining the study will be collected if given.

6.5. Subsequent follow-up

Follow up data will be collected by postal, electronic or telephone questionnaires.

Follow up 1: Up to 4 weeks after study registration – this will be conducted by electronic, telephone or postal questionnaire. Questions are unconfirmed at this time (awaiting results of stages 1 and 2), but are likely to be:

1. Current clinical status
2. Examination findings

Follow up 2 and 3: At 4 and 9 months – will be conducted by postal, electronic or telephone questionnaire.

Questions will be:

1. Foot and Ankle Outcome Score (FAOS)[8]
2. Health service resource use
3. Health related quality of life (EuroQuol EQ-5D)[9]

6.6. Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospectively having been overlooked at screening)
- Significant protocol deviation
- Withdrawal of Consent
- Loss to follow up

The reason for withdrawal will be recorded in the Study Withdrawal Form.

We will use a small financial incentive (£5) in the form of vouchers at the 9 month follow up only in order to maximise the follow up rate. This will improve the scientific quality of the study, and save time and effort in chasing non-returned questionnaires by the study team. [10]

6.7. Discontinuation/Withdrawal of a site

Recruitment and screening data will be monitored by the trial team. This will also be reviewed by the Trial Management Group and the Study Steering Committee (SSC). Where necessary, after appropriate support, if a site has persistent low recruitment a site may be required to close and resources used to establish another site.

Participants that have agreed to take part in the Dynamic Consent study will be able to access their consent choices online, and change their mind regarding certain aspects of the study, for example whether they would like to be contact by email or not. Participants that want to change their preferences will visit the website and select the appropriate option to indicate that they would like to withdraw from a specific aspect of the study, or change how they wish to be contacted. There will be a 'cooling off period' of 7 days for withdrawal choices, and the research team will receive a notification of this decision, to allow them to follow up with the participant. After 7 days the participant will have formally withdrawn from the specific aspect of the study. Participants will also be able to withdraw from the Dynamic Consent part of the study, without withdrawing from SPRAINED at any point during the study, and in this case their online profile will be deleted following the 7 day cooling off period.

6.8. Definition of End of Study

The end of study is the dates of the last 9 month follow up of the last study participant, if follow up is possible.

6.9. Serious Adverse Events

No Serious adverse events/adverse events are anticipated as no treatment is being delivered as part of the SPRAINED Study.

7. STATISTICS AND ANALYSIS

7.1. Description of Statistical Methods

Outcome that we will predict:

The key factors that signify a poor outcome after ankle sprain are poor function, instability of the joint, which is typified by recurrent sprains and or a significant lack of confidence in the ankle (a persistent feeling of giving way), with or without chronic pain. There is good consensus in international guidance that any of these outcomes would merit further investigation and intervention.

For the development dataset we will define poor outcome at 9 months as either

- Moderate or severe persistent pain
- Moderate or severe functional difficulty
- Significant lack of confidence in the ankle
- Recurrent sprain

These items were collected by self-report in the CAST study. The selection of these variables as outcome indicators is supported by evidence from van Rijn[11] who reported recovery was most closely associated with improvements in pain and giving way. Wikstrom et al[4] report pain and instability are of greatest concern to patients. We have examined the CAST data set and the event rate is 30%. Given the event rate and number of predictors we will carry forward, we have more than adequate numbers for modelling.

The performance of the tool will be assessed using calibration and discrimination metrics. Calibration will be assessed graphically with results for patients grouped by similar probabilities (tenths) and compare the mean predicted probability to the mean observed outcome.[12 13] The calibration plot will also be supplemented with estimates of the calibration slope and intercept. The discrimination of various prognostic models will be summarised with the concordance index (equivalent to the Area Under Receiver Operating Characteristic curve) with 95% confidence interval.

Additional predictors not contained in the development dataset will be examined to see whether they improve the performance of the prognostic model using net reclassification improvement (NRI) and integrated discrimination improvement (IDI).[14]

Neither calibration nor discrimination captures the clinical usefulness of the prediction model (i.e. how does using the prediction model improve on a default policy of no prediction model). This will be examined using decision curve analysis, a relatively novel yet increasingly recommended approach in evaluating the predictive performance of a prediction model. It calculates the net benefit of using the model compared to not using the model,[15] evaluating and determining ranges of cut-off values for decision-making. The approach permits evaluation of the tools over a range of thresholds and the model

with the greatest net benefit (i.e. the number of true positives penalised by a weighted proportion of the false-positives) will be considered as the preferred prediction model. The results will be converted into 'an additional x patients per 1000' who would be identified using the prediction tool compared to not using the tool. If additional predictors are found to be helpful, we will evaluate the incremental value of the predictors and update the model to accommodate these accordingly.[13 16] A model with the greatest net benefit (i.e. the number of true positives penalised by a weighted proportion of the false-positives) will be considered as the preferred prediction model.[15]

As part of the validation of the prognostic tool, we shall identify and evaluate the tool in pre-defined subgroups to evaluate the usefulness of the model in these subgroups. These subgroups will have different case-mix and thus if the model is shown to be useful in these subgroups, it increases the likelihood the model will be generalizable to other untested subgroups (e.g. primary care).[17]

8. DATA MANAGEMENT

8.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations. All data and documentation will be stored in accordance with regulatory requirements and access to the data will be restricted to authorised study personnel. Oxford Clinical Trials Research Unit (OCTRU) will securely hold the database.

For the Dynamic Consent part of the study, participants will have access to their secure electronic personal profile with a username and password. SPRAINED trialists will have access to a separate portal that will provide an overview of the SPRAINED participants that are using Dynamic Consent; the trialist will be able to see the external trial ID. Names and email addresses will not be visible to anyone other than the participant. Data available to trialists will thus be anonymous.

8.2. Data Recording and Record Keeping

Baseline data will be collected from participants and/or the research team and recorded on a paper Clinical Dataset Form and prognostic tool. Data will also be collected for the three study follow up time frames (up to 4 weeks, and at 4 and 9 months, from study registration), and will be via post or via telephone call for collection of core data. Where necessary secure online data collection may take place for the 4 week timeframe.

Baseline Clinical Dataset Forms will be sent by a member of the local research team to the study coordinating office in Oxford by post, using a Freepost account. Follow up CRFs will be sent by the participant to the study coordinating office in Oxford by post, using a Freepost account. Where telephone follow up is used, a member of the central study team will carry out data collection directly onto the follow up CRF.

Upon receipt of questionnaires/CRFs, appropriate data quality and validation checks will be carried out and the data entered into a study-dedicated database which is developed and maintained by OCTRU, a UKCRN Registered Clinical Trials Unit. OpenClinica software will be used. To identify

manual entry errors a 10% double entry check will be carried out at regular intervals during the data collection phase of the study.

Study documentation must be retained for 5 years after completion of study-related activities. Collaborating sites are delegated the responsibility of archiving local essential documents (including the Investigator Site File) in an appropriate secure environment. The study office will archive the central Trial Master File and associated documents according to University of Oxford policy and this may include the use of an external professional archiving site.

All data will be processed according to the Data Protection Act 1998, and all documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name. Identifiable contact information will be stored separately from study data.

For the dynamic consent element of the study, the participant portal will cease to be available to participants 6 months after the completion of the SPRAINED study. The trialist portal will be formally handed over to the OCTRU team and will remain active for the length of time that the SPRAINED data is retained.

9. QUALITY ASSURANCE PROCEDURES

The study may be monitored or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures. A Monitoring Plan will be developed according to OCTRU's SOPS which involves a risk assessment. The monitoring activities are based on the outcome of the risk assessment and may involve central monitoring and site monitoring.

10. ORGANISATION

10.1. Project timetable and milestones

The aim is to recruit 675 patients to the trial over a period of 10 months.

10.2. Study Steering Committee

The Study Steering Committee (SSC) provides overall supervision of the trial on the behalf of the funder and is chaired by an Independent Member. The SSC abides by the OCTRU Standard Operating Procedure and the OCTRU SSC Charter which is based on the MRC Clinical Trials Unit template. The SSC will monitor study progress and conduct and advise on scientific credibility. Meetings of the SSC will take place at least once a year during the participant recruitment period.

10.3. Study Management Group

The Study Management Group (SMG) is made up of the Investigators listed on the front of this protocol, and staff working on the project within OCTRU and the Critical Care Trauma and Rehabilitation Trials Group. This group will oversee the day-to-day running of the trial and will meet regularly.

10.4. Local Co-ordination

Each participating site will identify a local Principal Investigator and local research clinician (as necessary). The responsibility of local research clinicians will be to:

1. Be familiar with the trial
2. Liaise with the SPRAINED coordinating team in Oxford
3. Disseminate SPRAINED protocol and information to staff involved in the trial locally
4. Ensure mechanisms are in place to facilitate the recruitment of eligible patients, monitor recruitment locally and identify barriers to recruitment and work towards solving them
5. Ensure timely consenting of patients
6. Work with local Research and Development staff to facilitate approvals
7. Deal promptly with missing data queries and return these to the study office
8. Facilitate other aspects of local collaboration as appropriate
9. Make all data available for verification, audit and inspection purposes as necessary
10. Ensure participant confidentiality is respected by all persons at all times
11. The PI at each site will identify local staff who will be responsible for delegated duties. The Delegation Log should be updated accordingly. New staff should be trained and added to the log as the study progresses. When the Delegation Log is updated, a copy should be sent to the study coordinating office in Oxford. The Delegation Log is part of the ISF and must be updated when any responsibilities are delegated locally. A copy of the updated version of the log must be sent to the study office.

11. ETHICAL AND REGULATORY CONSIDERATIONS

11.1. Declaration of Helsinki and Good Clinical Practice

This trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and the applicable requirements as stated in the Research Governance Framework for Health and Social Care (2nd edition 2005). Local investigators must ensure the study is conducted in accordance with relevant regulations and with Good Clinical Practice.

11.1.1. Ethics approval

The study can only start after approval from one of the Health Research Authority Ethics Committee, and once local Trust management approvals are in place. The protocol and patient facing documents/advertising material will be submitted to an appropriate Research Ethics Committee (REC), and host institution(s) for written approval.

The Sponsor will also review study documents prior to ethics submission, the Sponsor for the study is: University of Oxford.

The Chief Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

The REC has the purpose to look after the rights, well-being and dignity of patients. The REC reference number is given on the front page of this protocol. The NHS REC that reviewed this study was the London and Chelsea REC committee.

11.1.2. Local approvals

The study office will assist collaborating sites with the necessary approvals to allow the study to take place within their Trust. Typically this involves the submission of a Site Specific Information electronic form via the on-line Integrated Research Application System, and a signed contract between the Sponsor and the local site's Research and Development Office. Once these approvals are in place the study office will inform the local Principal Investigator of the date the study can open to recruitment at their site.

11.2. Reporting

The CI shall submit once a year throughout the study or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties. In addition, the funder requires regular Progress Reports throughout the study period.

11.3. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

Personal data required for the study will be collected directly from trial participants and hospital notes after consent. All personal information received in paper format for the trial will be held securely and stored separately from any data collected and only accessed by authorised personnel. The consent form includes consent for this data to be held. All staff involved in the study share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be entered and stored on a password protected access restricted secure server at the University of Oxford under the provisions of the Data Protection Act and/or applicable laws and regulations.

12. FINANCE AND INSURANCE

12.1. Funding

The SPRAINED study funding has been awarded by the NIHR HTA Programme (project number 13/19/06).

Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA, NIHR, NHS or the Department of Health.

12.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

13. TRIAL REGISTRATION

The SPRAINED study is registered on publically available databases on the internet:

1. The International Standard Randomised Controlled Trial Number (ISRCTN) Registry: The ISRCTN for SPRAINED is ISRCTN12726986
   http://www.isrctn.com/ISRCTN12726986

2. UK Clinical Research Network Study Portfolio Database: Database ID 18977
   http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=18977

14. PUBLICATION POLICY

Data from this study should not be presented in public or submitted for publication without requesting consent from the Study Steering Committee.

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the NIHR HTA programme. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

The Chief Investigator will coordinate dissemination of data from this study. All publications using study data from the main analyses will be submitted to the SSC for review before release.

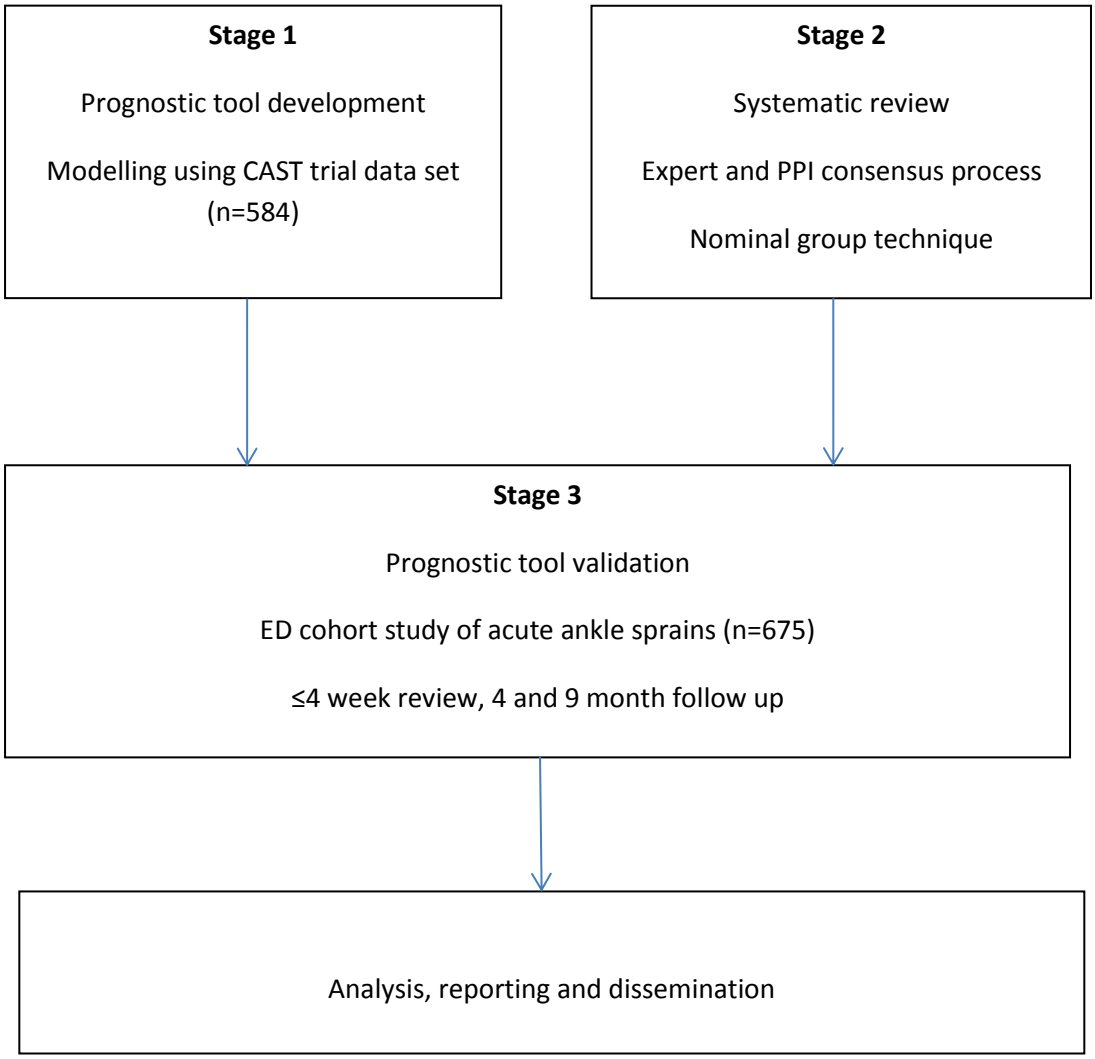
We will provide all participants with a summary of the trial outcome.

15. REFERENCES

1. Cooke M, Marsh J, Clark M, et al. Treatment of severe ankle sprain: a pragmatic randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of three types of mechanical ankle support with tubular bandage. The CAST trial. Health Technol Assess 2009;**13**(13):iii, ix-x, 1-121.
2. van Rijn RM, van Os AG, Bernsen RM, et al. What is the clinical course of acute ankle sprains? A systematic literature review. Am J Med 2008;**121**(4):324-31.e6.

3. Polzer H, Kanz KG, Prall WC, et al. Diagnosis and treatment of acute ankle injuries: development of an evidence-based algorithm. Orthop Rev (Pavia) 2012;**4**(1):e5.
4. Wikstrom EA, Hubbard-Turner T, McKeon PO. Understanding and treating lateral ankle sprains and their consequences: a constraints-based approach. Sports Med 2013;**43**(6):385-93.
5. Verhagen RA, de Keizer G, van Dijk CN. Long-term follow-up of inversion trauma of the ankle. Arch Orthop Trauma Surg 1995;**114**(2):92-6.
6. Stiell I, Wells G, Laupacis A, et al. Multicentre trial to introduce the Ottawa ankle rules for use of radiography in acute ankle injuries. Multicentre Ankle Rule Study Group. BMJ 1995;**311**(7005):594-7.
7. van Dijk CN, Mol BW, Lim LS, et al. Diagnosis of ligament rupture of the ankle joint. Physical examination, arthrography, stress radiography and sonography compared in 160 patients after inversion trauma. Acta Orthop Scand 1996;**67**(6):566-70.
8. Roos EM, Brandsson S, Karlsson J. Validation of the foot and ankle outcome score for ankle ligament reconstruction. Foot & Ankle International 2001;**22**(10):788-94.
9. Brooks R. EuroQol: the current state of play. Health Policy 1996;**37**(1):53-72.
10. Edwards PJ, Roberts I, Clarke MJ, et al. Methods to increase response to postal and electronic questionnaires. Cochrane Database Syst Rev 2009(3):MR000008.
11. van Rijn RM, Willemsen SP, Verhagen AP, et al. Explanatory variables for adult patients' self-reported recovery after acute lateral ankle sprain. Phys Ther 2011;**91**(1):77-84.
12. Steyerberg EW. *Clinical prediction models: a practical approach to development, validation, and updating*: Springer, 2009.
13. Harrell FE. *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis*: Springer, 2001.
14. Pencina MJ, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;**27**(2):157-72; discussion 207-12.
15. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;**26**(6):565-74.
16. Sullivan LM, Massaro JM, D'Agostino RB. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. Stat Med 2004;**23**(10):1631-60.
17. Altman DG, Royston P. What do we mean by validating a prognostic model? Stat Med 2000;**19**(4):453-73.
18. Peduzzi P, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;**49**(12):1373-9.
19. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007;**165**(6):710-8.
20. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. Stat Med 2006;**25**(1):127-41.
21. Royston P, Sauerbrei W. Building multivariable regression models with continuous covariates in clinical epidemiology--with an emphasis on fractional polynomials. Methods Inf Med 2005;**44**(4):561-71.
22. Vergouwe Y, Royston P, Moons KG, et al. Development and validation of a prediction model with missing predictor data: a practical approach. J Clin Epidemiol 2010;**63**(2):205-14.
23. O'Connor SR, Bleakley CM, Tully MA, et al. Predicting functional recovery after acute ankle sprain. PLoS One 2013;**8**(8):e72124.
24. van Middelkoop M, van Rijn RM, Verhaar JA, et al. Re-sprains during the first 3 months after initial ankle sprain are related to incomplete recovery: an observational study. J Physiother 2012;**58**(3):181-8.

16. APPENDIX A: STAGES OF THE SPRAINED STUDY



17. APPENDIX B: COHORT STUDY SUMMARY

SPRAINED STUDY

Synthesising a clinical Prognostic Rule for Ankle INjuries in the Emergency Department

A Cohort Study to externally validate a prognostic tool developed in the early stages of SPRAINED

A minimum of 5 NHS EDs and MIUs will participate in recruiting patients for approximately 10 months. Sites with a target recruitment rate of approximately 15 patients per month will be selected.
675 patients attending EDs and MIUs will be recruited. The initial approach will be made by a member of the ED/MIU clinical team upon presentation in the ED/MIU. An oral explanation of the study along with a study information leaflet will be given to all potentially eligible patients. Posters to display in the departments will be provided.

Participant's eligibility:

Inclusion Criteria:

- Participant is willing and able to give informed consent for participation in the study
- Male or Female, aged 16 years or above
- Diagnosed with acute ankle sprain (≤ 7 days old)

Exclusion Criteria:

- Ankle fracture (excluding flake fracture ≤ 2mm)
- Other recent (≤ 3 months) lower limb fracture

The informed consent process will be carried out by a qualified health care professional with delegated authority from the Principal Investigator. We anticipate in most sites this will be a research nurse/Allied Health Professional who will be a part of the local Clinical Research Network team.

Prognostic tool used at:

1. Initial attendance (patient or ED clinician completion)
2. Up to 4 weeks after study registration via online/postal/telephone questionnaire

Participant Questionnaire:

1. At 4 months after study registration
2. At 9 months after study registration

4 and 9 month follow up may be carried out by online, post or telephone questionnaire. Each participant remains in the study for a total of 9 months.

18. APPENDIX C: SUMMARY DESCRIPTION OF STAGES 1 AND 2

Stage 1: Developing a multivariable prognostic model from the CAST dataset for assessment of risk of poor outcome.

CAST is the largest trial of interventions for moderate to severe ankle sprains to date (worldwide), by a considerable margin (n=584).[1] Professor Sallie Lamb was Chief Investigator of CAST which followed up between 584 and 441 participants depending on the point of follow up. There is data on a comprehensive number of predictors, including those identified as potentially important by clinical guidelines/consensus and in previous multivariable analyses. The central research team have data at ED presentation, 3 to 5 days later, then at 1, 3 and 9 months. Variables will be identified for the prognostic tool using multivariable logistic regression modelling and will model the impact of a review at about five days. The CAST study had full ethical and governance approvals and consent taken covers intended use of the data.

There is currently no consensus on the best approach to developing a prediction model, however, the early stages of the SPRAINED study will use a transparent process that implements appropriate statistical methods and adheres to current methodological recommendations.[12 13] Up to 15 candidate predictor variables will be chosen for inclusion in a multivariable logistic regression model (recovered or not). Simulation studies examining predictor variables for inclusion in logistic regression models suggest at least 10 events per candidate predictor to avoid over fitting,[18] whilst others have suggested this figure could be as low as 5.[19] A backwards selection procedure will be used to select which of the candidate predictor variables should be included in the final prediction model (with $p < 0.2$ conservatively taken to warrant inclusion and prevent over fitting). All continuous predictors will be kept as continuous in the modelling to avoid any loss in power (e.g. by dichotomising).[20] Any continuous predictors exhibiting a nonlinear relationship with the outcome will be considered for modelling using fractional polynomials.[21] There is missing data in the CAST data set, although the baseline predictor set is near complete, and final follow up is greater than 76%. To avoid excluding patients and thereby reducing the sample size, multiple imputation will be used to impute missing values, under a missing at random assumption.

The number of available predictors plausibly related to the outcome could be as many as 30. The number of predictors for inclusion into the multivariable modelling will be reduced by examining whether predictors can be combined (due to multicollinearity), based on either subject knowledge, statistical clustering techniques, complexity measurement and completeness of measurement.[13 22] Predictors will also be considered for omission if the distribution of the predictor is narrow, thereby unlikely to contain sufficient predictive information and face-validity.

A series of models will be run to compare the inclusion of objective clinical examination variables supplementary to self-report items, as well as the added value of additional information at different time points. The utility of the 4 week data from the CAST dataset will be explored to replicate findings of previous prognostic models generated from the baseline and follow up data of clinical trials.[23 24] A targeted approach at 4 weeks will be evaluated to see if this is helpful (for example picking up those who self-report persisting problems).

Internal validation, score and format derivation

Models will be internally validated using bootstrapping, and adjusted for over fitting. The presentation of various models will be simplified to a scoring system.[13 16] This can be more challenging than initially appears, but the help of PPI reps and clinical colleagues will be enlisted in developing a rational tool for clinical/patient self-completion.

The prognostic models will produce a risk score (probability) for each patient. The statistical measures of calibration or discrimination do not capture the clinical usefulness of the prediction model (i.e. how does using the prediction model improve on a default policy of no prediction model). This will be examined using decision curve analysis, which calculates the net benefit of using the model compared to not using the model,[15] evaluating and determining ranges of cut-off values for decision-making.

Stage 2a: Systematic review of the literature

A systematic review will be conducted to identify risk factors for poor outcome following acute ankle sprain to identify any additional variables that should be considered in the external validation study.

Stage 2b: Expert consensus process

A Modified Nominal Group Technique will be used to gain consensus and information on preferences. Briefing papers will be prepared containing lay summaries of the findings of the modelling elements completed in Stage 1 and findings regarding additional predictive factors from the systematic review in stage 2a. The consensus element will be achieved by a face-to-face meeting in small groups, with independent facilitation, and a pre-specified set of questions (determined once stages 1 and 2a are complete). Two steps will be used in this process, the first one for identification of issues and general discussion and the second for resolution and consensus.

Participants - 12 clinicians (including ED doctors, trauma/sports physicians, physiotherapists, ED nurses, and MIU staff) and 12 patient representatives (representing a range of age, gender, and physical activity/sport participation) will participate.

19. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	11Nov2015	Dr Mark Williams	Added information on Dynamic Consent bolt-on study
2	3.0	03Mar2016	Dr David Keene	Clarification that follow-up time points are from study registration
3	4.0	28Jul2016	Mr Daryl Hagan (Clinical Trials Administrative Coordinator)	Addition of electronic/online methods of data collection taking place for all follow up time points.