CLINICAL STUDY PROTOCOL

Management of acute lateral ankle sprains: A randomized, controlled trial

Principal Investigator:	Christian Olsen, PT, MSc., PhD Candidate
Investigators:	Marius Henriksen, PT, PhD, Professor Søren Thorgaard Skou, PT, PhD
Sponsor:	Department of Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospitals.
NCT ID:	Not yet assigned
Unique Protocol ID:	SJ-628
Date:	3/5 2018

1.0 STUDY COMMITTEES

Protocol Development Committee:

Name	Title & Position	Affiliation
Christian Olsen	PT, MSc, PhD Candidate	Næstved-Slagelse-Ringsted Hospitals
Marius Henriksen	PT, PhD, Professor	Bispebjerg-Frederiksberg Hospital
Søren Thorgaard Skou	PT, PhD, Head of Research	Næstved-Slagelse-Ringsted Hospitals
Mikael Elsborg	PT	The Regional Hospital in Horsens

2.0 FLOW CHARTS

2.1 Enrollment process

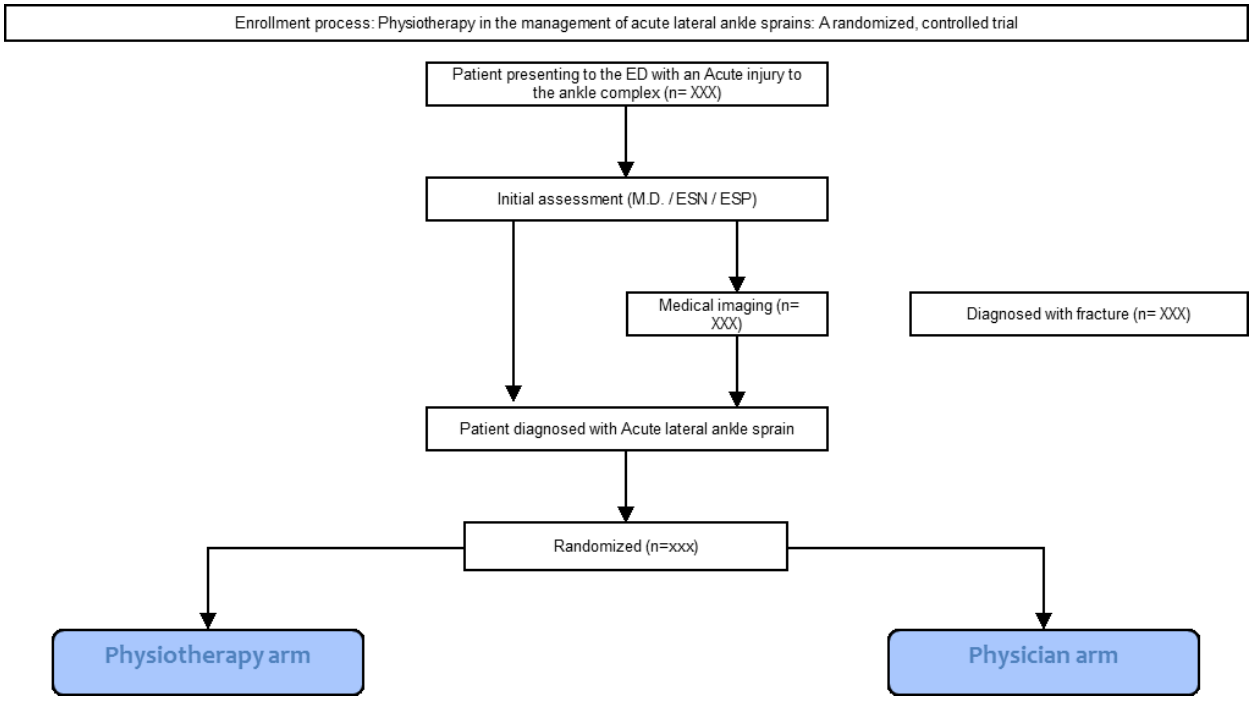

Figure 1 Enrollment process

2.2 Study flow chart

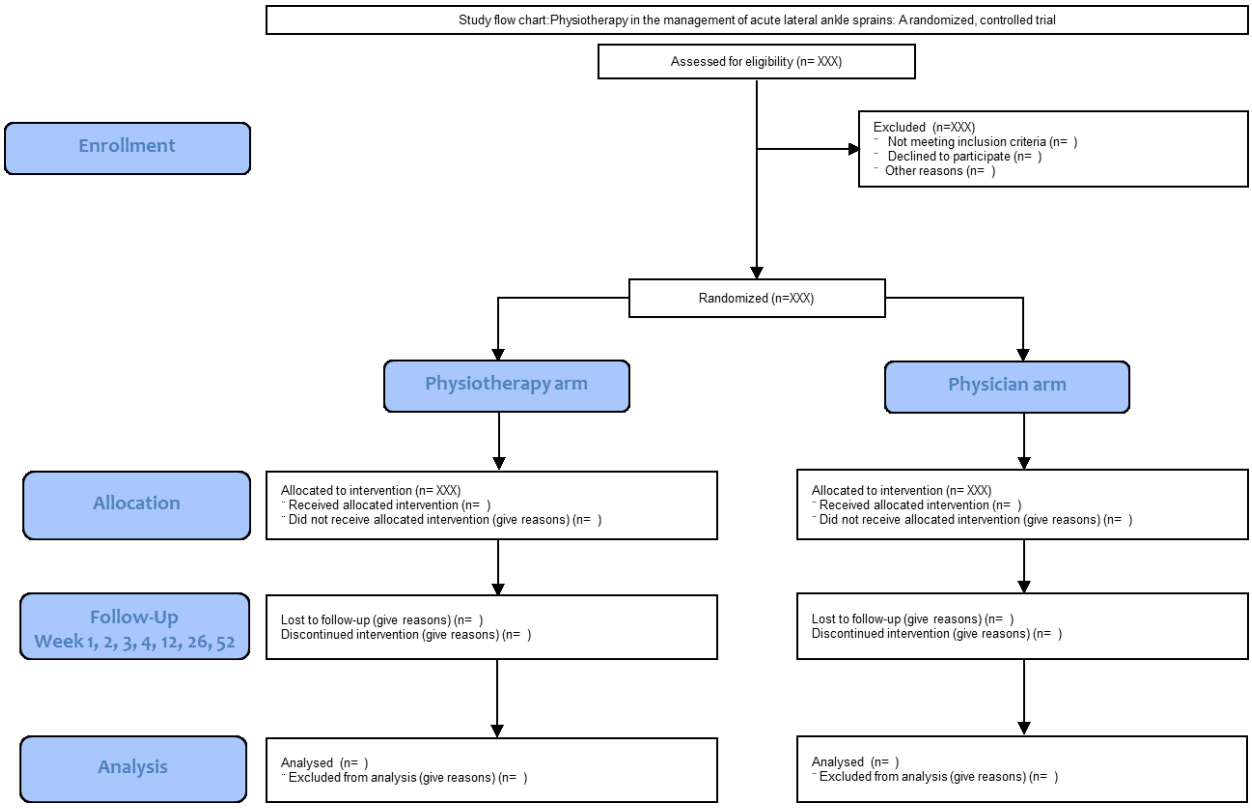

Figure 2 Study flow chart

2.3 Visit schedule

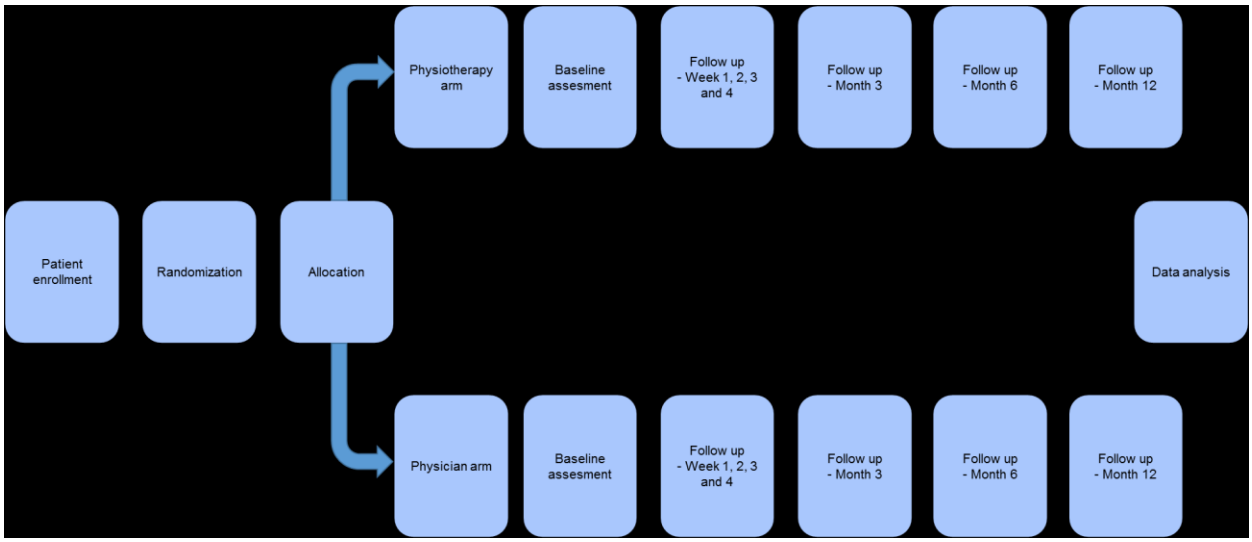

Figure 3 Visit schedule

3.0 TABLE OF CONTENTS

4.0 TRIAL IDENTIFIER

4.1 Full title of trial

Management of acute lateral ankle sprains: A randomized, controlled trial

4.2 Short title

Management of acute lateral ankle sprains

4.3 Acronym

Pending

4.4 Health Research Ethics Committee Number

SJ-628

4.5 Trial registration identifier and date

Pending

4.6 Version number and date

Version 1.0 (first draft for committee review; pre-authorisation version)

Version 1.1 (Updated with changes, as specified by the secretary, before presentation to the health research ethics commitee)

Version 1.2 (Updated with changes, as specified by the regional health research ethics committee)

Version 1.3 (Updated with changes, as specified by reviewers from www.clinicaltrials.com)

4.7 Revision history

Version #	Issue date	List of major changes
1.0	May 29, 2017	This is the first draft
1.1	June 8, 2017	All questionnaires will be translated to Danish before trial start. The Study will be carried out following "The Act on Processing of Personal Data" All positive, negative or inconclusive results will be published at www.clinicaltrials.gov.

1.2	July 25, 2017	Mikael Elsborg is included in the study committee. The economic properties for this study is included in the written information.
1.3	May 3, 2018	Translated all information to English before publication on www.clinicaltrials.com. Updated the first page to include the unique Human Subjects Review board number: SJ-628 and date. Finn Erland Nielsen has withdrawn his participation in this study and thus removed from the protocol development committee.

4.8 Sponsor

The Department of Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospitals.

5.0 BACKGROUND INFORMATION

Lateral ankle sprains (LAS) is the most common injury in the active population [1–4]. Not only is the injury prevalent within organized sports, but also display high prevalence in the general population presenting at the emergency departments (ED) [2,5]. LAS accounts for about 3-5% of all visits to the ED, but total LAS incidence rates are increasing in the general population[6–10].

Acute LAS is defined by Delahunt et al.[8] and endorsed by the International ankle consortium[9] as: *"An acute traumatic injury to the lateral ligament complex of the ankle joint as a result of excessive inversion of the rear foot or a combined plantar flexion and adduction of the foot."* The treatment of LAS in the emergency department consists of initial assessment and acute management of the injured foot, traditionally done by a physician. The typical assessment consists of ruling out severe injury, i.e. fracture, using the Ottawa ankle foot rules [10,11]. The acute management of the injured ankle is typically composed of a treatment approach consisting of Rest, Ice, Compression and Elevation (RICE).

Extended Scope of Practice (ESP) physiotherapists in EDs have shown to generate high levels of patient satisfaction[12,13], reduce patient waiting times[14] and have high clinical effectiveness[13], yet high quality randomized trials investigating the clinically effectiveness of ESP physiotherapy are lacking. Acute LAS is one of the most common injuries managed in EDs and poor functional status within the initial 2 weeks after injury is predictive of development of chronic ankle instability (CAI)[15], which can be a serious barrier for future physical activity and occupational performance. Early and targeted interventions provided in the emergency department by ESP physiotherapists may therefore prove to be beneficial for the patients and the society.

We therefore propose this trial that aims to assess the effectiveness of ESP physiotherapy as a mean to enhance the outcome of acute LAS following presentation to an emergency department.

6.0 STUDY HYPOTHESIS

6.1 Hypothesis

The functional outcome following presentation to an ED with an acute LAS is superior when managed by an ESP physiotherapist compared to usual procedures.

7.0 STUDY DESIGN

7.1 Description of the protocol

This is a randomized, pragmatic, superiority study with 1, 2, 3 and 4 weeks, and 3, 6 and 12 months of follow-up (figure 2). The study will be carried out in the emergency department at 2

large public hospitals in Slagelse and Horsens, Denmark. Two-hundred-twenty-six adults with an acute lateral ankle sprain will be included in this study.

The participants will be randomly allocated to one of two treatment strategies:

> **Strategy A**: A single session with advice and instructions from an ESP physiotherapist in rest, ice, compression and elevation AND pain guided early weight bearing plus a written home-based exercise program (ESP physiotherapy group).

or

> **Strategy B**: A single session with advice and instructions from a physician in rest, ice, compression and elevation (usual care).

The randomized allocation will be equal (1:1).

7.1.1 Justification of a pragmatic trial design

The pragmatic trial design has the benefit of making employees and decision-makers in the emergency department aware of the protentional benefits in early weight bearing and exercise in the large group of people presenting with an acute LAS. Participants receiving information and advice from a physiotherapist in the emergency department, will be giving instructions in early weight bearing and exercise and the participants receiving usual care will not, because it is the effects of these two strategies, when administered in the emergency department, we want to compare. The pragmatic design means that the trial will provide valuable information that will help clinicians and decision-makers decide if advice from a physiotherapist in the emergency department improves the clinical outcomes of acute LAS.

7.2 Duration of study participation

The study's duration is 12 months after randomization.

8.0 SELECTION AND ALLOCATION OF PARTICIPANTS

8.1 Number of participants planned

It is anticipated that 226 participants will be enrolled in this study. A participant may be enrolled in this study provided he/she has met all the inclusion criteria and has not met any of the exclusion criteria.

8.2 Inclusion Criteria

An individual will be eligible for study participation if he/she meets the following criteria:

1. A grade 1 or 2 LAS sustained within 24 hours of randomization
2. To be a minimum age of 18
3. Signed informed consent

8.3 Exclusion Criteria

A participant will be excluded from the study if he/she meets any of the following criteria:

1. A grade 3 LAS injury sustained
2. Diagnosed with chronic ankle instability (CAI) on the affected limb
3. Fracture diagnosed by X-ray
4. Previous enrollment in the same study
5. Major lower limb surgery or other severe lower extremity injury in the past 3 months on the affected limb
6. Under the influence of drugs or alcohol
7. A condition that, in the opinion of the investigator, would preclude participation in the study (e.g., not having access to the internet, immobilization etc.)

8.3.1 Grading of LAS

The grading of each patient is following Standard Operating Procedures (S.O.P.) (Appendix 1).

1.° LAS (At present the patient can bear weight)

2.° LAS (Pronounced limping, major pain)

3.° LAS (The patient cannot bear weight on the foot)

8.3.2 Chronic ankle instability

The participant should report a minimum of one major LAS injury sustained a minimum of 12 months prior to assessment for eligibility of enrolment in the study. After this injury, the participant should have experienced the classical signs of decreased function and swelling.

Participants should report at least two episodes of 'giving way' or have sustained two or more ankle sprains to the same ankle in the 6 months prior to the study enrolment to be diagnosed with CAI [9].

We endorse the definition of giving way as: *"The regular occurrence of uncontrolled and unpredictable episodes of excessive inversion of the rear foot (usually experienced during initial contact during walking or running), which do not result in an acute lateral ankle sprain"* [8].

8.4 Allocation of participants and sequence generation

We will stratify the randomization by

- Site (2 levels; Slagelse Hospital and The Regional Hospital in Horsens)

The allocation ratio will be 1:1.

Randomization lists will be computer-generated based upon permuted random blocks of variable size (3 to 6 in each block).

8.5 Blinding

Data analysts will be blinded to treatment allocation.

9.0 TREATMENTS

9.1 Usual care

Participants allocated to usual care (Strategy B) will receive instructions in managing their acute LAS accordingly to the S.O.P. at the site (Appendix 1). These guidelines consist of advice provided by the physician at work in; Rest, Ice, Compression and Elevation. Avoiding new stretches/ sprains for a few months after the injury is advised and gradually putting more weight on the ankle, progressing to running and twisting.

9.2 Physiotherapy

Participants allocated to ESP physiotherapy (Strategy A) will receive instructions on how to manage their acute LAS and a written homebased exercise program by an ESP physiotherapist. The instructions on how to manage their acute LAS will consist of written and oral advice. The protocol consists of advice in accelerated weight bearing, already at discharge. It is advised to bear weight and exercise with pain up to, but not exceeding, VAS 5. The written homebased exercise program should be initiated at discharge from the hospital. When patients are experiencing pain exceeding VAS 5 they will follow the same guidelines as the usual care group consisting of Rest, Ice, Compression and Elevation.

Compression, with an elastic bandage, is administered in the ED and instructions on how to apply and manage the bandage correctly, will be given. The bandage should be worn all day, including at night for 3 weeks. The elastic bandage should also be worn as protection when performing exercises and activities that increases the risk of reinjury for a minimum of 3 month after injury.

9.2.1 ESP physiotherapy

An ESP Physiotherapist is a clinical physiotherapy specialist with an extended scope of practice. This implies working beyond the recognized scope of physiotherapy practice, for example requesting investigations e.g. X-rays; using the results of investigations to assist clinical diagnosis and appropriate management of patients; and referring to other professionals. The ESP physiotherapist will have a minimum of 2 years of relevant clinical experience in assessment, diagnosing and treating of patients with minor musculoskeletal injuries. The ESP physiotherapist has taken or are currently enrolled in supplementing their basic professional training with additional courses in musculoskeletal physiotherapy.

9.2.2 Exercise program for the physiotherapy group

The exercise program from baseline to 4 weeks follow-up will consist of ankle rehabilitation exercises focusing on walking with full weight bearing, neuromuscular training, balance training, muscle strengthening and jumping. The participants will be asked to perform the exercises on a daily basis. The exercises should be performed with pain up to but not exceeding 5 on an 0-10 VAS pain scale. If the patient experience VAS pain ≥6 he/she should follow the standard guidelines of rest, ice, compression and elevation. The patient will receive information on how to perform the exercises by the ESP physiotherapist and an exercise program will be

handed out in the ED (Appendix 2). A link will be sent to the participants with the same exercise program including online videos describing the exercise in detail.

9.3 Concomitant Therapy

Participants will be asked to register the type and frequency of any concomitant therapy. There will be no restrictions in concomitant therapy.

10.0 OUTCOME ASSESSMENTS/VARIABLES

10.1 Primary Outcome

10.1.1 Lower extremity functional scale

The primary outcome measure is the change from baseline in the Lower extremity functional scale (LEFS)[16] assessed at 4 weeks after randomization. LEFS will also be assessed at 1, 2 and 3 weeks, and 3, 6 and 12 months, these timepoints will be regarded as secondary outcomes.

The Lower extremity functional scale is a self-completed questionnaire providing a total score based on the patients subjective ankle function. The scale consists of 20 functional leg activities, each scored on a five point scale (0 impossible, 4 no difficulty), giving a minimum score of 0 (worst) to 80 (best). The questionnaire will be translated into Danish using a dual-panel approach before trial start. The LEFS will be scored online by the trial participant. This approach avoids the requirement for follow-up visits in a clinic.

10.2 Secondary outcomes

The following secondary outcomes will be measured, at baseline and the 1, 2, 3 and 4 weeks, and 3, 6 and 12 months follow-ups, unless stated otherwise. All of the secondary outcomes will be scored online by the trial participant. This approach avoids the requirement for follow-up visits in a clinic.

10.2.1 Pain at rest and with activity, assessed using a visual analogue scale (VAS)

The pain VAS is a unidimensional measure of pain intensity, which has been widely used in diverse adult populations[17,18]. The scale is a continuous scale comprised of a horizontal line,

anchored by 2 verbal descriptors, one for each symptom extreme (0 no pain, 10 the worst imaginable pain). We will measure pain VAS at rest and pain VAS with activity.

10.2.2 Foot and ankle ability measure (FAAM)19

The FAAM scale is a region-specific outcome instrument divided in two separate subscales, the FAAM activities of daily living (adl) and the FAAM Sports subscales. Evidence of validity to support the use of the FAAMadl and FAAMsport is available in individuals with a wide array of ankle and foot disorders19–21. The questionnaire will be measured at 1, 2, 3 and 4 weeks, and 3, 6 and 12 month follow-ups and used in secondary analysis. The questionnaire will not be measured at baseline. The questionnaire will be translated into Danish using a dual-panel approach before trial start.

10.2.3 The Cumberland ankle instability tool (CAIT)[22]

The CAIT is a simple, validated, and reliable tool to measure severity of functional ankle instability[9,22]. The CAIT consists of 9 questions that are answered separately for the right and left ankle. It is scored on a 30-point scale, with lower scores indicating decreased stability. The minimal clinically important difference (MCID) for patients with chronic ankle instability is ≥3 points[23]. The questionnaire will be translated into Danish using a dual-panel approach before trial start.

10.2.4 Reinjury rates

Reinjury rates will be recorded during follow-up assessments at weeks 1-4 and 3-12 months. We endorse the definition of an ankle sprain as: *"An acute traumatic injury to the lateral ligament complex of the ankle joint as a result of excessive inversion of the rear foot or a combined plantar flexion and adduction of the foot. This usually results in some initial deficits of function and disability"*[8,9]. Reinjury will not be considered as a stopping rule for further participation in this study. Reinjures will be measured at 1, 2, 3 and 4 weeks, and 3, 6 and 12 month follow-ups and used in secondary analysis.

10.2.5 Quality of life (EQ-5D-3L)[24]

The EQ-5D-3L is a measure of current health status developed by the EuroQol Group for clinical and economic appraisals. The questionnaire consists of five questions assessing five

dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension is rated on three levels: no problems, some problems and extreme problems.

10.2.6 Global perceived effect (GPE)[25]

Perceived effect of treatment will be measured using a transition questionnaire (TRANS-Q) on which the participants will answer if their current LAS-related health status is "unchanged", "worse" or "better" compared to their pre-LAS status. An "unchanged" equals a transition score of 0. If the participant answers "worse", he/she is asked to rate the degree of worsening on a 7 point Likert scale, and the corresponding scores range from -1 to -7. If a participant answers "better", he/she is asked to rate the degree of improvement on a 7 point Likert scale, and the corresponding scores range from 1 to 7.

10.2.7 Patient acceptable symptom state (PASS)[26]

The PASS is the value beyond which patients consider themselves well. Patients' opinions of their state will be recorded by answering ''Yes'' or ''No'' to the question: ''Taking into account all the activities you have during your daily life, your level of pain, and also your functional impairment, do you consider your current state is satisfactory?''.

10.2.8 Analgesic use

The participants self-reported use of analgesics will be collected at baseline and at follow-up week 1-4. Participants will be asked to note their use of analgesic drugs within the week before baseline and the follow-up.

10.3 Data collection methods

For consenting patients, we will at Baseline collect data on age, height, body weight, previous lateral ankle sprain, limb dominance, injured limb left/right, time since injury, education, employment, patient's contact details (Appendix 4). The information will be derived using an online platform on an Ipad available in the emergency department. Baseline data will be collected after randomization, but before treatment, E.g. in the waiting room after medical imaging.

The questionnaires will be sent to the participants in the study at 1, 2, 3 and 4 weeks and 3, 6, and 12 months. The data will be collected using an internet-based platform (Easytrial), with personal links sent to the participants on the day the window for follow-up opens. The window for completion of data registration will be small during the first 4 weeks allowing only a ±2-day registration window. At the 3, 6 and 12-month follow-up, reminders will be sent one and two weeks before and one week after the follow-up date. This will give a window of 4 weeks for completion of the assessments. See Appendix 7 for a copy of the covering letters.

To improve response rates participants will be offered the option of completing the questionnaires in paper versions to be returned by post. We will send pre-notification messages/emails/letters.

11.0 DISCONTINUATION

11.1 Participant withdrawal

As this is a study performed in the emergency department, participants will not be able to have a 24-hour consideration period before inclusion in the study. We consider the study and its procedures to be justified from a health research ethics perspective. There are no risks or predictable harms associated with this approach.

A participant is advised to contact the investigators by telephone if they wish to withdraw from the study. A participant will be able to withdraw at any time point throughout the study period without this impacting on any future investigations and/or treatments.

If a participant withdraws from the study, the primary and secondary outcomes are sought collected before discontinuation.

11.2 Discontinuation of clinical sites

The Sponsor has the right to terminate the participation of a clinical site at any time. Reasons may include the following, but are not restricted to:

- The incidence of events at the site that indicate a potential health hazard to participants and which is not considered sporadic (i.e. events could be expected to occur at other sites as well).
- Unsatisfactory participant enrolment at the site.
- Unsatisfactory data completeness at the site.

- The incidence of protocol violations at the site which is not considered sporadic or very severe (i.e. events could be expected to occur at other sites as well).

11.3 Discontinuation of Entire Study

The Sponsor has the right to terminate this study at any time. Reasons may include the following, but are not restricted to:

- The incidence of events in this or other studies that indicate a potential health hazard to participants.
- Unsatisfactory participant enrolment.

12.0 STUDY PROCEDURES

12.1 Trial related clinical visits

There will be no trial-related clinical assessments. Follow-up will be done only via internet-based assessments.

12.2 Assessment windows

The assessment windows are as follows:

- Baseline measurements will be taken after randomization but before treatment in the ED.
- Outcome assessment at 1, 2, 3 and 4 weeks can be taken within ± 2 day for the scheduled assessment
- Outcome assessments at 3, 6, and 12 months can be taken within ± 2 weeks before or after the scheduled assessment.

12.3 Baseline assessment

Baseline tests and procedures must be performed and reviewed before allocation. The following information/assessments will be collected at the baseline visit:

1. Inclusion/exclusion criteria review
2. Collection of baseline information (Appendix 4)

3. Collection of primary and secondary outcomes
4. Randomization

12.4 Study completion

The end-of-study is defined as the date of the last participant's last scheduled assessment, 12 months after enrollment.

12.5 Collection of data from hospital records

All relevant information on participants will be collected using online Case Report Forms (CRF). No additional information will be collected from the included participant's hospital records.

13.0 DETERMINATION OF SAMPLE SIZE AND STATISTICAL ANALYSIS PLAN

13.1 Determination of Sample Size

The study will be powered to detect a difference in change of 9 points between the two groups in the primary outcome (LEFS) from baseline to 6 months follow-up. The 9 point change has previously been recommended and applied in similar studies as the minimal clinically important difference in LEFS[27]. To detect this difference, we will need 94 patients in each group (assuming a common SD of 19, power = 90%, alpha level = 0.05). We plan to recruit 226 patients to account for loss to follow-up (20%).

13.2 Participants description

13.2.1 Disposition of Participants

The total number of randomized participants will be summarized by site using counts and percentages. The number of patients either completing or discontinuing the study will be summarized using counts and percentages.

13.3 Study Population definitions

13.3.1 Intention to treat population (ITT)

The ITT population consists of all randomized patients regardless of whether the patient received study intervention or failed to comply with the study protocol, in the treatment group to which the participant was assigned (see Figure 2).

13.3.2 Per protocol (PP)

The per protocol population consists of participants in the ITT population with a valid baseline measurement of the variable to be analyzed.

13.3.3 As-observed population (AO)

The AO population consists of participants who has the outcome of interest assessed at a given time point of interest (i.e. no imputation of missing data will be done).

13.4 Data analysis considerations

The primary outcome is change from baseline in the lower extremity functional scale and will be analyzed using the ITT population.

13.5 General statistical approach

For quantitative variables we will calculate mean, standard deviation, median, range and number of missing data.

All summary tables for qualitative variables will display counts, percentages and number of missing data (if relevant) by treatment group.

All statistical tests will be two-sided and statistical significance will be claimed if the computed p-value is equal to or less than 0.05.

13.5.1 Concomitant medication and/or therapy

The use of concomitant medications and/or therapies (e.g. GP consultations, physiotherapy, etc.) will be summarized in each treatment group.

13.6 Primary analysis

13.6.1 Primary outcome analysis

The primary endpoint is the change from baseline in the lower extremity functional scale at the 4-week follow-up. The primary analysis will be done on the ITT population.

13.6.2 Data transformation before analysis, if any

No data transformation will be applied to raw data.

14.0 STUDY COMMITTEES

14.1 Protocol Development Committee

14.1.1 Membership

The Protocol Development Committee of this study is composed of scientific, technical, and administrative persons from participating sites and other collaborating participants. There are no restrictions to the number of members in the committee.

14.1.2 Roles and responsibilities

This committee, led by its chairman Christian Olsen, is responsible for development, refinement, and finalization of this protocol and planning of activities related to the study.

This study was conceptualized by Christian Olsen (Study Chairman and principal investigator). The initial version of the protocol (version 1.0) was developed by Christian Olsen.

14.2 Executive Committee

The research group consists of the PhD student Christian Olsen M.Sc. in physiotherapy who will be the central study coordinator and principal investigator. Christian Olsen has experience as an ESP in the ED at Slagelse Hospital.

Marius Henriksen, Professor of Physiotherapy at the University of Copenhagen. Marius Henriksen has a special interest in research in musculoskeletal injuries and diseases and has experience with the implementation of large multicenter studies.

Søren Thorgaard Skou, PhD Physiotherapist, head of research at the Department of Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospitals. Søren has experience with the design, conduct and reporting of RCT studies and coordinating large multicenter cohorts in musculoskeletal conditions.

Finn Erland Nielsen is head of Research and Chief Physician in the emergency department at Slagelse Hospital. Finn Nielsen has clinical epidemiology, register based research and emergency medicine as main interests. He has acquired a doctorate in medicine and a master degrees in applied statistics and public management. Finn Nielsen is research supervisor for doctors and medical students and has been assessor of a large number of PhD theses'.

Mikael Elsborg, physiotherapist, is managing the ESP physiotherapists working at The Regional Hospital in Horsens. He has a great interest in collection of data, and working with research projects. Mikael will be responsible for the coordination of data collection at the Horsens site in this study.

15.0 ETHICS

15.1 General considerations

Prior to assessment for eligibility the trial participants will be informed, both orally and in writing, about the purpose of this trial, the overall duration and potential risks, as well as costs and benefits for participation. The leaflet "*Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt*" will be handed out and participants will be encouraged to read it before trial enrolment. All participants are informed of their rights to withdraw from the study. The participant may withdraw oral, written or with other clear indications about the attend to resign from the research project. If the participant withdraws their consent, this will not affect their right to present or future treatment or any other rights they may have. After the information is delivered, read and understood, voluntary informed consent is given by the participant by signing a consent form before trial participation can take place.

15.2 Oral information

When a potential participant is identified during initial assessment in the ED he/she will be given information about this trial. If further investigations are needed to determine eligibility for enrollment, the information will be given after completion of these. It will be stressed that the investigator is asking the participant to consider participation in the trial, and that the potential

trial participant has the right to bring a companion to the information interview, if possible. The written information material will be handed out in the ED by the trial investigator. The participants will not be able to have a 24-hour consideration period before inclusion in the study, but will have sufficient time to consider inclusion. The oral information will be given in a language easily understood without technical or value-laden terms. The information will be given in a considerate way that is tailored to each potential trial participants. The conversation will take place without interference. It is the responsibility of the interviewer to ensure that the potential trial participant has understood all the information giving. Guidelines for the oral information are given in Appendix 6.

15.3 Written information

A written information material has been prepared and is attached this protocol as Appendix 5.

15.4 Informed consent

Consent to participation in the trial is given on the basis of the written and oral information. An informed consent form (Appendix 8) has been prepared. The form must be signed and dated by the participants prior to participation in the trial. A copy of the form is provided to the participants. The investigator or his designated delegates can receive the signed consent form.

15.5 Research ethics -the interventions

15.5.1 Physiotherapy

The study will be conducted in accordance with the Helsinki declaration and follow ICH9 Good Clinical Practice guidelines. We consider the study and its procedures to be justified from a health research ethics perspective. There are no risks or predictable harms associated with the physiotherapy intervention that at worst are considered harmless.

15.5.2 Usual care

As this is defined as usual clinical care it is not considered to be associated with research ethical issues.

15.6 Research ethics – the outcome measures

15.6.1 Questionnaires

Questionnaires are not considered to be associated with research ethical issues.

15.7 Research ethics approval

The study will be conducted in accordance with Danish law, the Helsinki declaration, and local research ethics committee requirements.

The Sponsor is responsible for keeping the ethical committee informed of amendments or changes to the protocol, and the progress of the study.

16.0 CASE REPORT FORM COMPLETION

16.1 Case Report Forms

The study will use electronic CRFs using an online web-based clinical trial management application (EasyTrial). EasyTrial allows individual patients to supply data from home.

The application meets all regulatory standards, and allows management of all activities related to clinical trials that ensures optimal resource use and safety according to good clinical practice and data protection legislation.

17.0 REGULATORY STANDARDS

This study will be conducted in accordance to the Danish law: *"The Act on Processing of Personal Data"*.

17.1 Notification to the Danish Data Protection Agency

Because the study is carried out at hospital emergency departments, it is regarded as "public" in accordance with the Data Protection Agency guidance. The study will be notified to the Data Protection Agency before trial start.

17.2 Financing and insurance information

The study is funded by:

The Department of Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospitals.

The Research Unit at Næstved, Slagelse and Ringsted Hospital.

18.0 PUBLICATION

This study will be published in a peer-reviewed journal. In addition, the results will be presented at international conferences.

In addition, the results will be regularly presented at an Annual National Seminar on ESP physiotherapists in the emergency room, arranged by the Department of Physiotherapy and Occupational Therapy, Næstved-Slagelse-Ringsted Hospitals, Region Zealand.

All positive, negative or inconclusive results will be published at www.clinicaltrials.gov.

19.0 INVESTIGATOR'S AGREEMENT

1. I have read this protocol and agree that the study is ethical.
2. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
3. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Investigator name (printed) Date & Signature

Christian Olsen_____

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Marius Henriksen_____

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Søren T. Skou_____

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Finn Erland Nielsen_____

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20.0 REFERENCE LIST

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21.0 APPENDICES

21.1 Appendix 1 – S.O.P.

Standard operating procedure

DS93.4	DISTORSIO REGIONIS MALLEOLI	1.° distorsion (At present the patient can bear weight): **RICE** 2.° distorsion (Pronounced limping, major pain. Able to walk 4 steps): **RICE + Pain management** 3.° distorsion (The patient cannot bear weight on the foot and walk 4 steps): **RICE+ crutches +pain management**	No follow-up Follow-up at general practitioner

21.2 Appendix 2 – Exercise program

Afdeling for Fysio- og ergoterapi

Exercise program after acute lateral ankle injury (EN)

By: Christian Olsen

EXORLIVE

It is recommended that You immediately start this training program. It is advised to exercise with pain up to, but not exceedig 5 on a pain-scale (0-10). 0 represents no pain and 10 represents the worst pain you can imagine. If you experience pain of 6 or more, You must follow the RICE principles until the pain again is below 5.

1. Information

This training program should be followed daily the first 4 weeks after your acute lateral ankle sprain. The training program is designed to be performed in the morning, at noon and in the evening.
You can use an ice bag as pain reliever. Place it directly on top of the the damaged area for 10 minutes. Pull it of and wait 10 minutes. Continue until the pain is improved.

2. Walking forward as a figure of eight movement

Walk forward and form a figure of eight. Return to starting position and repeat. Start walking in a large figure of eight, about 10 meters.
At each minute decrease the figure of eight by 1 meter, thus the last minute is only 1 meter long.
You have to walk with a speed that gives you pain corresponding to 5 or less on the 0-10 pain-scale. You are alloved to jog / run. Exercise each day in the morning, at noon and in the evening.

Sets: , Duration: 12 min 0 sec, Pain level: 5 0-10

3. One Leg Jump in Circle, Both Ways

Stand on one leg on a mat with your hands in your side. Do a 90 degrees jump on the mat and continue jumping till you have jumped all the way around yourself. Then jump 90 degrees in the opposite direction and continue till you have jumped all the way around yourself again.

Sets: , Reps: 12 , Pain level: 5 0-10

4. Single leg stand on a balance cushion (knees bent)

Stand on a pillow (or fold a mat and stand on that). Stand on one leg with the knee a little bend. Hold the other leg out in the air and grab a hold of your hips with your hands. Try to keep your balance.

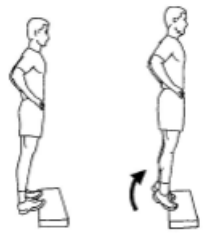
Tid: 12 min, Sets: , Pain level: 5 0-10

Play Program

Afdeling for Fysio- og ergoterapi

Exercise program after acute lateral ankle injury (EN)

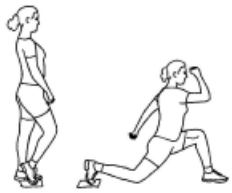
By: Christian Olsen



5. Toe lift on bench or step

Stand on the edge of a step or a bench so that your heels are free, feet about hip-width apart. Raise your heels and push up until you are on your toes. Return to the start position and repeat. The exercise can be done with or without support.

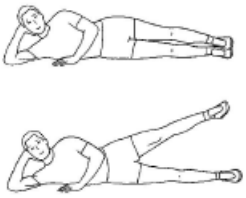
Reps: 12 , Sets: , Pain level: 5 0-10



6. Gradual Backwards Lunge

Focus on a spot in front of you. Tighten your abdomen, place one foot on the mat and move backwards. Lower your back knee down towards the floor. Press your bottom down towards the floor, tighten abdomen and move your leg back to starting position. Perform the exercise with both legs.

Sets: , Reps: 12 , Pain level: 5 0-10



7. Side-lying single leg lift 2

Lie on your side with straight legs, supporting your head with one hand. Raise your top leg. Ensure that your toes point straight forward and that only your hip is moving. You should therefore avoid tilting your pelvis toward you or rotating your hip. Repeat the exercise with your other leg. Perform the exercise with both legs.

Sets: , Reps: 12

21.3 Appendix 3 – Outcomes

We are interested in knowing whether you are having any difficulty at all with the activities listed below because of your lower limb problem for which you are currently seeking attention. Please provide an answer for **each** activity.

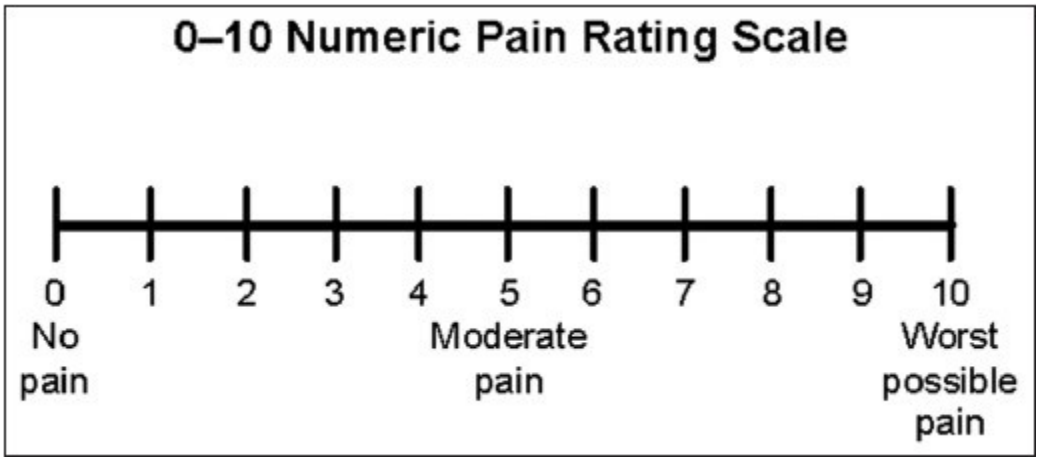
Today, do you or would you have any difficulty at all with:

(Circle one number on each line)

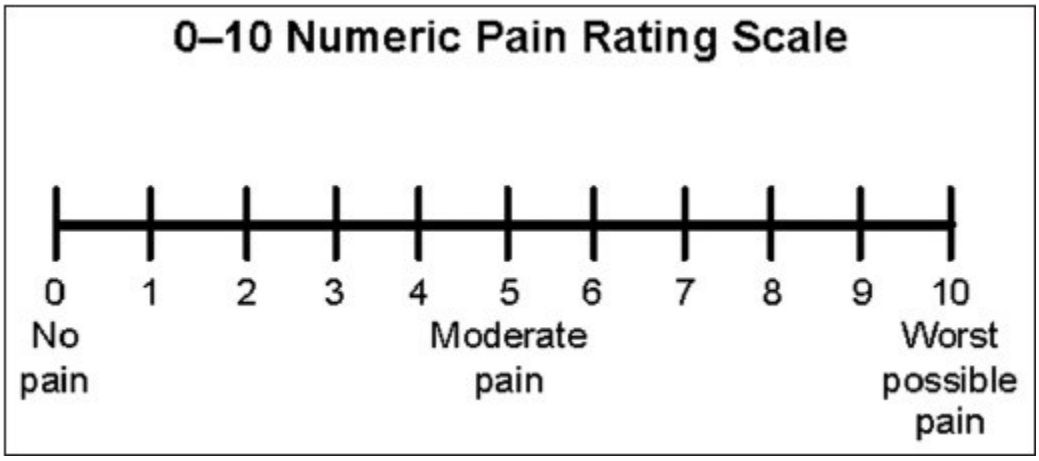
Activities	Extreme Difficulty or Unable to Perform Activity	Quite a Bit of Difficulty	Moderate Difficulty	A Little Bit of Difficulty	No Difficulty
a. Any of your usual work, housework, or school activities.	0	1	2	3	4
b. Your usual hobbies, recreational or sporting activities.	0	1	2	3	4
c. Getting into or out of the bath.	0	1	2	3	4
d. Walking between rooms.	0	1	2	3	4
e. Putting on your shoes or socks.	0	1	2	3	4
f. Squatting.	0	1	2	3	4
g. Lifting an object, like a bag of groceries from the floor.	0	1	2	3	4
h. Performing light activities around your home.	0	1	2	3	4
i. Performing heavy activities around your home.	0	1	2	3	4
j. Getting into or out of a car.	0	1	2	3	4
k. Walking 2 blocks.	0	1	2	3	4
l. Walking a mile.	0	1	2	3	4
m. Going up or down 10 stairs (about 1 flight of stairs).	0	1	2	3	4
n. Standing for 1 hour.	0	1	2	3	4
o. Sitting for 1 hour.	0	1	2	3	4
p. Running on even ground.	0	1	2	3	4
q. Running on uneven ground.	0	1	2	3	4
r. Making sharp turns while running fast.	0	1	2	3	4
s. Hopping.	0	1	2	3	4
t. Rolling over in bed.	0	1	2	3	4
Column Totals:					

SCORE: _____/80

Figur 4 - Lower extremity functional scale (English version).



Figur 5 - VAS Pain scale with rest



Figur 6 - VAS Pain scale with activity

Foot and Ankle Ability Measure (FAAM)
Activities of Daily Living Subscale

Please Answer **every question** with **one response** that most closely describes your condition within the past week.
If the activity in question is limited by something other than your foot or ankle mark "Not Applicable" (N/A).

	No Difficulty	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Standing	☐	☐	☐	☐	☐	☐
Walking on even Ground	☐	☐	☐	☐	☐	☐
Walking on even ground without shoes	☐	☐	☐	☐	☐	☐
Walking up hills	☐	☐	☐	☐	☐	☐
Walking down hills	☐	☐	☐	☐	☐	☐
Going up stairs	☐	☐	☐	☐	☐	☐
Going down stairs	☐	☐	☐	☐	☐	☐
Walking on uneven ground	☐	☐	☐	☐	☐	☐
Stepping up and down curbs	☐	☐	☐	☐	☐	☐
Squatting	☐	☐	☐	☐	☐	☐
Coming up on your toes	☐	☐	☐	☐	☐	☐
Walking initially	☐	☐	☐	☐	☐	☐
Walking 5 minutes or 1ess	☐	☐	☐	☐	☐	☐
Walking approximately 10 minutes	☐	☐	☐	☐	☐	☐
Walking 15 minutes or greater	☐	☐	☐	☐	☐	☐

Foot and Ankle Ability Measure (FAAM)
Activities of Daily Living Subscale
Page 2

Because of your foot and ankle how much difficulty do you have with:

	No Difficulty at all	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Home responsibilities	☐	☐	☐	☐	☐	☐
Activities of daily living	☐	☐	☐	☐	☐	☐
Personal care	☐	☐	☐	☐	☐	☐
Light to moderate work (standing, walking)	☐	☐	☐	☐	☐	☐
Heavy work (push/pulling, climbing, carrying)	☐	☐	☐	☐	☐	☐
Recreational activities	☐	☐	☐	☐	☐	☐

How would you rate your current level of function during you usual activities of daily living from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities.

__ __ __ . 0 %

Martin, R; Irrgang, J; Burdett, R; Conti, S; VanSwearingen, J: Evidence of Validity for the Foot and Ankle Ability Measure. Foot and Ankle International. Vol.26, No.11: 968-983, 2005.

Figur 7 - Foot and ankle ability measure ADL subscale (English version).

Foot and Ankle Ability Measure (FAAM)
Sports Subscale

Because of your foot and ankle how much difficulty do you have with:

	No Difficulty at all	Slight Difficulty	Moderate Difficulty	Extreme Difficulty	Unable to do	N/A
Running	☐	☐	☐	☐	☐	☐
Jumping	☐	☐	☐	☐	☐	☐
Landing	☐	☐	☐	☐	☐	☐
Starting and stopping quickly	☐	☐	☐	☐	☐	☐
Cutting/lateral Movements	☐	☐	☐	☐	☐	☐
Ability to perform Activity with your Normal technique	☐	☐	☐	☐	☐	☐
Ability to participate In your desired sport As long as you like	☐	☐	☐	☐	☐	☐

How would you rate your current level of function during your sports related activities from 0 to 100 with 100 being your level of function prior to your foot or ankle problem and 0 being the inability to perform any of your usual daily activities?

___ . 0%

Overall, how would you rate your current level of function?

☐ Normal ☐ Nearly Normal ☐ Abnormal ☐ Severely Abnormal

Martin, R; Irrgang, J; Burdett, R; Conti, S; VanSwearingen, J: Evidence of Validity for the Foot and Ankle Ability Measure. Foot and Ankle International. Vol.26, No.11: 968-983, 2005.

Figur 8 - Foot and ankle ability measure Sports subscale (English version).

APPENDIX 1: THE CAIT QUESTIONNAIRE

Please tick the ONE statement in EACH question that BEST describes your ankles.

	LEFT	RIGHT	Score
1. I have pain in my ankle			
Never	☐	☐	5
During sport	☐	☐	4
Running on uneven surfaces	☐	☐	3
Running on level surfaces	☐	☐	2
Walking on uneven surfaces	☐	☐	1
Walking on level surfaces	☐	☐	0
2. My ankle feels UNSTABLE			
Never	☐	☐	4
Sometimes during sport (not every time)	☐	☐	3
Frequently during sport (every time)	☐	☐	2
Sometimes during daily activity	☐	☐	1
Frequently during daily activity	☐	☐	0
3. When I make SHARP turns, my ankle feels UNSTABLE			
Never	☐	☐	3
Sometimes when running	☐	☐	2
Often when running	☐	☐	1
When walking	☐	☐	0
4. When going down the stairs, my ankle feels UNSTABLE			
Never	☐	☐	3
If I go fast	☐	☐	2
Occasionally	☐	☐	1
Always	☐	☐	0
5. My ankle feels UNSTABLE when standing on ONE leg			
Never	☐	☐	2
On the ball of my foot	☐	☐	1
With my foot flat	☐	☐	0
6. My ankle feels UNSTABLE when			
Never	☐	☐	3
I hop from side to side	☐	☐	2
I hop on the spot	☐	☐	1
When I jump	☐	☐	0
7. My ankle feels UNSTABLE when			
Never	☐	☐	4
I run on uneven surfaces	☐	☐	3
I jog on uneven surfaces	☐	☐	2
I walk on uneven surfaces	☐	☐	1
I walk on a flat surface	☐	☐	0
8. TYPICALLY, when I start to roll over (or "twist") on my ankle, I can stop it			
Immediately	☐	☐	3
Often	☐	☐	2
Sometimes	☐	☐	1
Never	☐	☐	0
I have never rolled over on my ankle	☐	☐	3
9. After a TYPICAL incident of my ankle rolling over, my ankle returns to "normal"			
Almost immediately	☐	☐	3
Less than one day	☐	☐	2
1–2 days	☐	☐	1
More than 2 days	☐	☐	0
I have never rolled over on my ankle	☐	☐	3

NOTE. The scoring scale is on the right. The scoring system is not visible on the subject's version.

Figur 9 - The Cumberland ankle instability tool (English version).

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

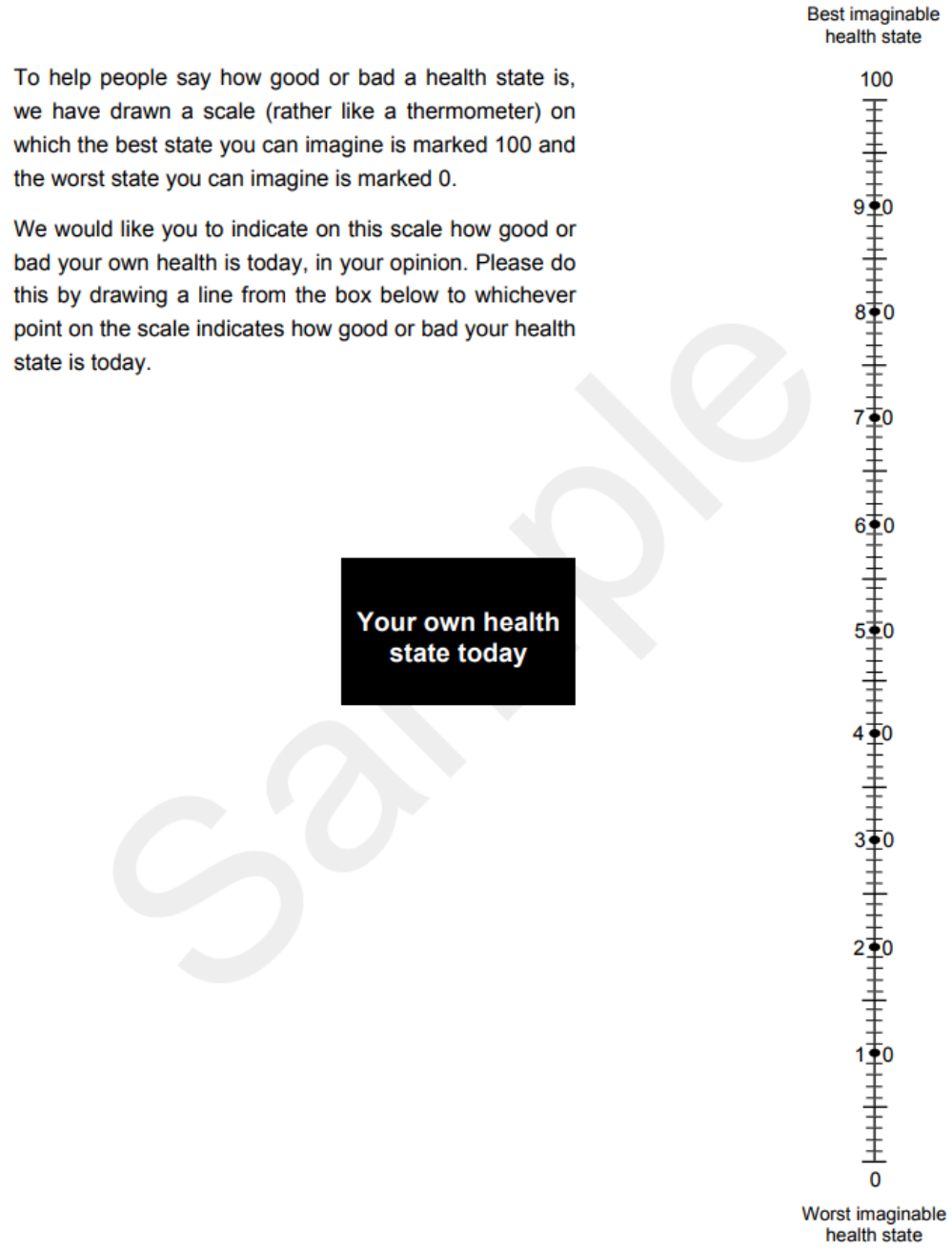
I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑



Figur 10 - EQ-5D-3L (Danish version)

21.4 Appendix 4 – Baseline form

Questions	Answers
Date of birth	Dd/mm/YYYY
Height	Cm
Weight	Kg
Previous lateral ankle sprain in the same ankle	Yes/No
Dominant leg	Left/Wright
Site of injury	Left/Wright
Time since injury	Hours/minutes
Years of education	Years
Yearly income	DKr.
Contact information	Address, Phone number, e-mail.

21.5 Appendix 8 – Informed consent form

(S1)

Informed consent form for participation in a health science research project.

Research project title: Management of acute lateral ankle sprains: A randomized, controlled trial

Statement by the subject:

I have received written and oral information and I know enough about the purpose, method, advantages and disadvantages to say yes to participate.

I know it is voluntary to participate and that I can always withdraw my consent without losing my current or future rights to treatment.

I agree to participate in the research project and have received a copy of this consent sheet as well as a copy of the written information about the project for its own use.

The subject's name: _____

Date: _____ Signature: _____

Do you want to be informed about the results of the research project and possible consequences for you?:

Yes _____ (Mark with X) No _____ (Mark with X)

Declaration by the person giving information:

I declare that the subject has received oral and written information about the trial.

In my conviction, sufficient information has been provided for a decision to participate in the trial.

The name of the person who provided information:

Date: _____ Signature: _____

Project identification:

Human Subjects Review board number: SJ-628