RESEARCH PROTOCOL

MUSCAT STUDY

PROTOCOL TITLE

MUlticenter randomized controlled trial on nonoperative versus operative treatment for acute complete tear**S** of the ulnar **C**ollateral lig**A**ment of the **T**humb: cost- effectiveness and functional outcomes.

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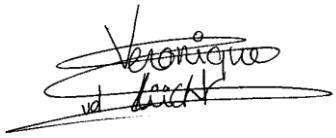
Coordinating Investigator MD Veronique van de Lücht *Department of Surgery Diakonessenhuis*		01-02-2024

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**
UCL	**Ulnar collateral ligament**

MHQ	**Michigan Hand Outcomes Questionnaire**
PSFS	**Patient Specific Functional Scale**
ED	**Emergency department**
RCT	**Randomized controlled trial**
SD	**Standard deviation**
MCID	**Minimal clinically important difference**
ISS	**Injury Severity Score**
CTS	**Carpal tunnel syndrome**
MCP	**Metacarpophalangeal**
CMC	**Carpometacarpal**
IP	**Interphalangeal**
ADL	**Activities of daily living**
ICHOM	**International Consortium for Health Outcomes Measurement International**
CUA	**Cost-utility analysis**
CEA	**Cost-effectiveness**
QALY	**Quality adjusted life year**

SUMMARY

Rationale: Guidelines recommend surgery for complete Ulnar Collateral Ligament (UCL) ruptures, including Stener lesions. This recommendation is based on expert opinion, anatomic theories and low quality observational case series. High quality studies comparing cast immobilization with operative treatment are lacking. We hypothesize that cast immobilization is non-inferior regarding functional outcome and carries concomitant lower costs compared with operative treatment for complete UCL ruptures, including Stener Lesions.

Objective: To compare functional outcomes and cost-effectiveness of cast immobilization with immediate surgical treatment.

Study design: Multicenter randomized controlled trial (RCT) with 12 months follow-up.

Study population: Adult patients of 18 years and above, requiring treatment for an acute complete UCL rupture, including Stener Lesions.

Intervention: Non-operative treatment with a cast to immobilize the thumb. After 2 weeks the thumb will be re-examined to determine if surgery is required. It is expected that at re-evaluation at 2 weeks after starting the cast treatment about 1 in 10 patients will still need surgery. The intervention is compared to surgery, which is standard treatment.

Main study parameters/endpoints: Hand function expressed as the Michigan hand outcome questionnaire (MHQ) score at 6 months (from date of injury to 6 months after).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: It is expected that about 1 in 10 patients who started with cast immobilization will need surgery during re-evaluation at 2 weeks after starting the cast immobilization, meaning completing the treatment will take 2 weeks more for these patients. Patients need to fill in questionnaires, which takes about 2 hours (maximum) over a period of 12 months.

1. INTRODUCTION AND RATIONALE

In the Netherlands, approximately 10,500 patients are diagnosed with an acute ulnar collateral ligament (UCL) injury of the thumb yearly. These UCL injuries are classified into 3 grades based on the laxity of the ligament. Grade 1 injuries present with tenderness along the UCL, without laxity compared with the non-injured thumb. They are classified as sprains and have an intact UCL. Grade 2 injuries demonstrate an increase in laxity, but have a firm endpoint which indicates a partial rupture of the UCL. Grade 3 injuries are complete UCL ruptures with increased laxity without a firm endpoint. Around 75% of UCL injuries are complete UCL ruptures. These complete UCL ruptures include Stener Lesions, meaning an interposition of a part of a thumb muscle between the torn ligament ends. The prevalence of Stener Lesions varies widely between studies, ranging from 11 to 87%. [1] Dutch guidelines drafted by the society of Surgery and Plastic Surgery, recommend immobilization of the thumb with a cast for 4-6 weeks for grade 1 and 2 injuries. For complete UCL ruptures, they recommend surgery followed by cast immobilization. This recommendation is based on expert opinion, anatomic theories and low quality observational case series, mainly level-IV evidence. High quality studies comparing cast immobilization with operative treatment are lacking.

Outcomes of surgery for complete UCL ruptures, including Stener Lesions, are generally good regardless of the surgical technique. Regarding nonoperative treatment, two observational studies that evaluated thumb immobilization with a cast for complete ruptures, including Stener Lesions, showed promising results: in 71 patients who underwent cast immobilization, 63 (89%) felt normal or had minimal disability after 1 year. Those who remained symptomatic were successfully treated with surgery. [2,3] One patient remained symptomatic after surgery (percentage is similar to patients treated with initial surgery). Taking those studies into account, a nonoperative treatment strategy for complete UCL ruptures, including Stener Lesions, after which patients only have a small chance of secondary surgery, could be justified. Nonoperative treatment with cast immobilization is minimal invasive and could lead to lower costs compared to operative treatment.

Therefore, we want to conduct a RCT with non-inferiority design comparing functional outcomes and cost-effectiveness of cast immobilization, only followed by operative treatment in case of persistent laxity after 2 weeks of cast immobilization, with immediate operative treatment.

2. OBJECTIVES

Primary Objective: to evaluate hand function expressed as the MHQ score at 6 months (from date of injury to 6 months after).

Secondary Objectives: to evaluate patient reported hand function and activities of daily life with the Patient Specific Functional Scale (PSFS) and MHQ, range of motion of the thumb joints, pinch/grip strength, pain, quality of life, patient satisfaction, patient expectation, complications, work-absence and cost-effectiveness up to 12 months.

3. STUDY DESIGN

Multicenter RCT to include 126 patients with 12 months follow-up to compare functional outcomes and cost-effectiveness of cast immobilization with surgical treatment. The study inclusion period is 30 months. Patients will be randomized by simple randomization. A flow diagram of the study is provided in figure 1.

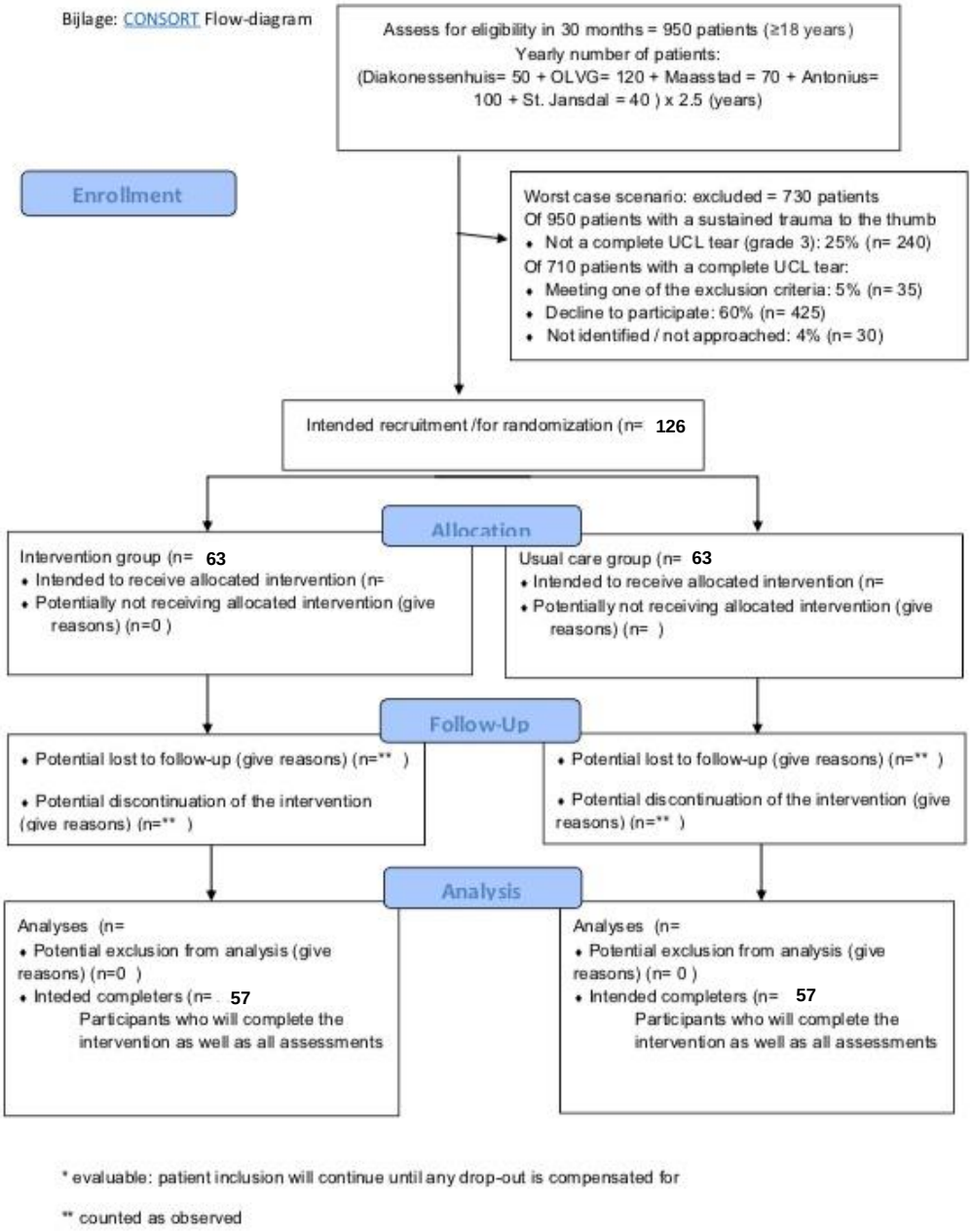

Figure 1.

4. STUDY POPULATION

4.1 Population (base)

Adult patients presenting at the emergency department (ED) with a sustained trauma to the thumb, resulting in acute pain and swelling around the MCP joint. The diagnosis of an acute complete UCL rupture, including Stener Lesions, needs to be confirmed by the surgeon by physical examination at the first outpatient clinic visit or directly at the ED

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Patients 18 years and older
- Dutch or English speaking patients
- Patients with an acute complete UCL rupture, with or without a Stener Lesion, diagnosed using physical examination, performed by the hand surgeon. When providing radically directed force to the proximal phalanx (radial deviation stress) as the thumb metacarpal is stabilized in a neutral position, criteria 1 AND 2 must be present to confirm the diagnosis of a complete UCL rupture:
    - no firm endpoint in the MCP joint AND
    - at least more than 35 degrees of laxity in the MCP joint, measured with the MCP joint in 30 degrees of flexion OR more than 15 degrees difference in laxity compared with the uninjured side.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Patients with a significant (> 15 of the articular surface) bone fragment on the radiograph.
- Patients with an additional fracture on the ipsilateral hand.
- Patients presenting to the ED with an UCL injury older than 13 days.
- Patients with a history of a UCL injury of the ipsilateral hand.
- Patients with impaired hand function prior to injury due to arthrosis/neurological disorders of the upper limb.
- Polytrauma patients (Injury Severity Score (ISS) = 16 or higher).
- Patients not able to give informed consent.

4.4 Sample size calculation

This sample size calculation is based on our primary endpoint (hand function at 6 months expressed as MHQ score 6 months after injury) and calculated using G Power 3.1.9.2. The MHQ score of an individual without any complaints of the hand is 100. The lowest score, indicating worst pain and severe impairment, is zero. The hypothesis will be assessed using a non-inferiority design. The results from two earlier studies on the subject were used for sample size calculation. [4,5] We used a one-sided significance level of 0.025 and a power of 80% with a standard deviation (SD) of 15, and setting our non-

inferiority limit at 8. The non-inferiority limit of 8 is based on the previous estimated minimal clinically important difference (MCID) of 15 points, divided by 2 and rounded up to 8. A total of 114 patients will be needed to demonstrate non-inferiority of our hypothesis. Each treatment arm will need 57 patients. Including consideration for a potential 10% loss to follow-up, the total number of patients to be included, set at 114, is multiplied by a factor of 1.10. This results in a total of 126 patients to be included.". The MCID of 15 is based on the average of the MCID's of 23, 13 and 8 for the pain, function and work domains, respectively in patients with carpal tunnel syndrome (CTS). [4] The MCID in MHQ score for patients with thumb injury is not yet investigated. Therefore, we decided to use the MCID of CTS patients.
Considering the uncertain outcome of the control group treatment in terms of MHQ-scores for patients with UCL-ruptures, an independent statistician will assess if the sample size calculation needs adjustment, based on the mean change in MHQ-score and SD in the control group, after half of the patients past their 6-month follow-up (N=28).

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

INTERVENTION
Patients in the intervention group receive non-operative treatment of the thumb using a cast to immobilize the metacarpophalangeal (MCP) and carpometacarpal (CMC) joint of the thumb in a neutral position for 4 weeks, followed by a removable cast for 4 weeks. During this time frame, the ruptured UCL ligament has a chance to heal. After 4 weeks of immobilization, all patients will be referred for hand therapy. The exact details of the treatment, from first presentation to full recovery, are described step-by-step.

1) First presentation at the ED (pre-treatment protocol)
This pre-treatment protocol applies to patients who present at the ED with a sustained trauma to the thumb, resulting in acute pain and swelling around the MCP joint of the thumb. These patients are potentially eligible for inclusion in the study and receive a temporary cast to immobilize the MCP and CMC joint of the thumb. An appointment with the surgeon is scheduled within 3-5 days from presentation at the ED.

2) First presentation at the outpatient clinic (start intervention)
During the first presentation at the outpatient clinic the surgeon (with sufficient experience in treatment of UCL injuries) confirms the diagnosis complete UCL rupture by physical examination. Laxity of the MCP joint is examined by providing radial force to the proximal phalanx, while stabilizing the thumb metacarpal bone. Stressing the MCP joint in the acute setting may be painful and guarding or muscle spasm may give a false-negative examination. Local anesthesia can be injected into the MCP joint to allow for better examination, when indicated. When the diagnosis of a complete UCL rupture is confirmed (according to the criteria provided under the inclusion criteria), the patient meets the inclusion criteria and has provided informed consent, the patient is randomized. Baseline outcome measures are evaluated in the form of surveys. If feasible at the study site, an ultrasound of the thumb is planned prior to application of a new cast to confirm the diagnosis for study purposes. The outcome of the ultrasound is blinded for the patients as well as for the surgeon. A new cast to immobilize the MCP, in 10-30 degrees (slight) flexion (neutral position), and the CMC joint, in 30-40 degrees palmar abduction, is applied (IP joint is free). Patients will be immobilized for a total period of 4 weeks, including the period between ED and outpatient clinic. After 4 weeks the immobilization cast will be replaced by a removable cast for a period of 4 weeks. Two weeks after the start of immobilization, a second appointment is scheduled to repeat examination of the thumb.

3) Repeat examination at the hand surgery outpatient clinic 2 weeks after ED visit.
Laxity of the MCP joint is re-examined by a hand surgeon. The hand surgeon examines if ‘tightening’ of the UCL has occurred by applying radial deviation stress to the dumb. The chance that re-examination at 2 weeks will induce a re-rupture or a Stener Lesion is close to zero, as re-examination at this time is also part of the current clinical practice in case of

cast immobilization. ‘Tightening’ is not a subtle finding and might even be present with less opening during radial deviation stress when compared to the contralateral thumb.

- When the hand surgeon concludes that there is a firm endpoint (meaning adequate healing of the UCL ligament) cast immobilization is continued for another 2 weeks, until a total immobilization period of 4 weeks is completed. An appointment is scheduled after 4 weeks of cast immobilization.
- When there is no firm endpoint of the UCL or there is doubt about a firm endpoint, patients are scheduled for surgery within 5 working days (switching to usual care; see description usual care).

4) Outpatient clinic visit after 4 weeks of immobilization
The patient visits the hand surgeon. The immobilization cast is removed and replaced for a removable cast, which allows the patient to start exercising. Patients are instructed to start using the thumb for regular daily activities, without putting pressure on it, and start thumb exercises consisting of a combination of opposition and abduction/adduction movements. Patients are advised to repeat the exercises 5-10 times a day. A referral is made to the hand therapist to guide this process. Hand therapy will start within 1 week. The frequency and duration of hand therapy will be determined by the hand therapist. Hand therapists from all hospitals will collaborate to achieve consensus on a treatment protocol. Outcome measures are evaluated in the form of physical examination and surveys. A new appointment is scheduled at 3 months.

5) Visit to outpatient clinic at 3 months (standard visit)
Progression of treatment is evaluated with the patient and expectations are managed. Outcome measures are evaluated in the form of physical examination and surveys. A new appointment is scheduled at 6 months.

6) Visit to outpatient clinic at 6 months (standard visit)
Progression of treatment is evaluated with the patient and expectations are managed
Outcome measures are evaluated in the form of physical examination and surveys. A new appointment is scheduled at 12 months.

7) Visit to outpatient clinic at 12 months (visit for study purpose)
Treatment outcome is evaluated for study purposes. Outcome measures are evaluated in the form of physical examination and surveys.

USUAL CARE/COMPARISON
The Dutch hand fracture guideline committee recommends operative treatment for patients with a complete UCL rupture, including Stener Lesions, and postoperative management with cast immobilization. [6] Patients will receive surgical treatment of the thumb. Postoperative management consists of cast immobilization of the MCP and CMC joint in neutral position for 4 weeks, followed by a removable cast for 4 weeks. The treatment details, from first presentation to full recovery are described step-by-step.

1) First presentation at the ER (pre-treatment protocol)
   This pre-treatment protocol applies to patients who present at the ED with a sustained trauma to the thumb, resulting in acute pain and swelling around the MCP joint of the thumb. These patients are potentially eligible for inclusion in the study and receive a temporary cast that immobilizes the MCP and CMC joint of the thumb.

Patients will be instructed not to use the thumb during this period. An appointment with the surgeon is scheduled within 3-5 days from presentation at the ED.

2) First presentation at the outpatient clinic (start treatment usual care)
During the first presentation at the outpatient clinic the surgeon confirms the diagnosis complete UCL rupture by physical examination. Laxity of the MCP joint is examined by providing radial force to the proximal phalanx, while stabilizing the thumb metacarpal bone. Stressing the MCP joint in the acute setting may be painful and guarding or muscle spasm may give a false-negative examination. Local anesthesia can be injected into the MCP joint to allow for getter examination when indicated. When the diagnosis of a complete UCL rupture is confirmed (according to the criteria provided under the inclusion criteria), the patient meets the inclusion criteria and has provided informed consent, the patient is randomized. Baseline outcome measures are evaluated in the form of surveys. Surgery is scheduled within 5 working days after the outpatient clinic visit. In the meantime, a new cast to immobilize the MCP and CMC joint is applied. If feasible at the study site, an ultrasound of the thumb is planned prior to surgery to confirm the diagnosis for study purposes. The outcome of the ultrasound is blinded for the patients as well as for the surgeon.

3) Surgery
In general, two surgical techniques are described in literature and used in daily clinical practice:

- If the UCL is ruptured in the middle of the ligament, sutures are used to reattach the ligament remnants together.
- When no viable UCL ligaments are present, the UCL is reattached directly to the bone using suture anchors.

Patients can choose between regional anesthetics of the upper arm or complete sedation. The procedure normally takes 30-45 minutes. Postoperatively, patients are treated with a cast immobilizing the CMC and MCP joint for 4 weeks followed by a removable cast for 4 weeks. After 10 days the skin sutures are removed at the outpatient clinic and the cast is renewed. [7]

4) Outpatient clinic visit 4 weeks after surgery
This part of the treatment protocol is identical to the protocol of the intervention group.

5) Visit to outpatient clinic at 3 months (standard visit)
This part of the treatment protocol is identical to the protocol of the intervention group.

6) Visit to outpatient clinic at 6 months (standard visit)
This part of the treatment protocol is identical to the protocol of the intervention group.

7) Visit to outpatient clinic at 12 months (visit for study purpose)
This part of the treatment protocol is identical to the protocol of the intervention group.

5.2 Summary of findings from clinical studies

Two systematic reviews are available on the treatment of complete UCL ruptures. [8,9] Both studies investigated nonoperative and operative treatment of patients with an acute complete tear of the UCL and concluded that no studies directly comparing nonoperative treatment with operative treatment were present. Regarding the current evidence, nonoperative treatment of complete UCL ruptures, including Stener Lesions, has been shown to be effective in most patients. [2,3] Although the ligament sometimes heals with slight laxity, there is no evidence for any benefits to surgery that outweigh the risks of nonoperative treatment.

Pichora et al observed 32 patients with a complete tear, with and without Stener Lesions, treated with bracing for 1 year. [2] Final laxity measured 2.3° on average; 91% of patients either felt normal or had minimal disability. Functional outcomes such as motion, timed dexterity, and grip and pinch strength measured 89% to 99% of the uninjured side. Three patients required secondary surgery. Landsman et al reported 6 out of 40 patients treated nonoperatively (15%) requested surgery, although they included several bony avulsions. [3]

The proposed intervention for complete UCL ruptures, including Stener Lesions, is a trial of cast immobilization with repeat examination after 2 weeks. There is no evidence that suggests that such a delay negatively affects the outcome if surgery is needed. Thumb immobilization of a complete tear is well described and frequently a successful method of treatment. However, qualitative, focused studies comparing cast immobilization with operative treatment are lacking.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

The Michigan Hand Questionnaire (MHQ), expressed as total MHQ score at 6 months (from date of injury to 6 months after) is the primary endpoint of the study. The MHQ is a validated tool for assessment of functional outcome in patients with pathology of the hand. The MHQ is a questionnaire divided in six subscales; overall hand function, activities of daily living (ADLs), pain, work performance, aesthetics and patient satisfaction with hand function. Each subscale has a formula to calculate a score. The final score is a summation of the six individual item-scores divided by six and goes from 0 (severe disability) to 100 (no disability). [10]

6.1.2 Secondary study parameters/endpoints

PATIENT REPORTED OUTCOME (PROM)
Since UCL injuries occur to patients of all ages, the expert panel advised to develop multiple communication channels for providing information and obtaining treatment data. Patients will have the choice to fill in the questionnaires between postal mail and online.

Besides the primary endpoint at 6 months from date of injury, the MHQ will be assessed at randomization, at 4 weeks of immobilization (when the immobilizing cast is replaced by a removable cast) and at 3 and 12 months from date of injury.

Patient-Specific Functional Scale (PSFS) is a self-reported, patient-specific outcome measure, designed to assess functional change, primarily in patients presenting with musculoskeletal disorders. Patients are asked to identify up to five important activities they are unable to perform or are having difficulty with as a result of their problem i.e. putting socks on. In addition to identifying the activities, patients are asked to rate, on an 11-point scale, the current level of difficulty associated with each activity. Following the intervention, patients are asked again to rate the activities previously identified and are given the chance to nominate new problematic activities that might have arisen during that time. “0” represents unable to perform, “10” represents able to perform. Patients select a value that best describes their current level of ability on each activity assessed. The PSFS will be assessed at randomization, after 4 weeks of immobilization (when the immobilizing cast is replaced by a removable cast) and at 3, 6 and 12 months from date of injury.

EQ-5D-5L is a measure of health-related quality of life that can be used in a wide range of health conditions and treatments. The EQ-5D consists of a descriptive system and the EQ VAS. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The EQ VAS records the patient’s self-rated health on a vertical visual analogue scale. This can be used as a quantitative measure of health outcome that reflects the patient’s own judgment. The score on the five dimensions can be presented as a health profile or can be converted into a utility score based on an available Dutch scoring algorithm (www.euroqol.org). The area under the curve of utility scores over time will be used to express the effect on quality of life in

QALY's. The EQ-5D-5L will be assessed at randomization and 2, 3, 6 and 12 months from date of injury.

The Numeric Pain Rating Scale (NPRS) will be used to assess pain, where 0 implies no pain and 10 the worst possible pain measured at randomization, after 4 weeks of immobilization (when the immobilizing cast is replaced by a removable cast) and at 3, 6 and 12 months after date of injury.

Patient satisfaction will be measured by using the ICHOM Satisfaction with treatment results questionnaire (self designed by ICHOM) measured at randomization, after 4 weeks of immobilization (when the immobilizing cast is replaced by a removable cast) and at 3, 6 and 12 months after date of injury.

The adapted Dutch institute for Medical Technology Assessment (iMTA) Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ) will be used to measure the amount of medical consumption, sick leave from work or lost productivity while at work and out-of pocket expenses due to a complete tear of the UCL and the questionnaires are adjusted for this study. A shortened version of the iPCQ including only questions about sick leave from work and lost productivity while at work is measured at baseline (at randomization). The full iMCQ and iPCQ will be measured at 2 (over the last 2 months), 3 (over the last month), 6 (over the last month, this will be multiplied by 3 for the cost effectiveness analysis), and 12 months (over the last month, this will be multiplied by 6 for the cost effectiveness analysis)) after injury.
Data will also be cross-verified with data from the Electronic Patient Record (EPD). If the data appears distorted, the analysis will be conducted using various scenarios to ensure its accuracy.

CLINICIAN REPORTED OUTCOME MEASURES (CROM)
Functional outcomes will be assessed by the head investigator of the study site to improve the reliability of measurements as much as possible. Before and during the study, multiple meetings will be scheduled with local investigators to optimize study logistics. All measurements will be performed as described in the International Consortium for Health Outcomes Measurement International (ICHOM) standard outcome set for hand and wrist conditions. [11]

Range of motion (ROM): flexion and extension of the metacarpophalangeal (MCP) joint and interphalangeal joint (IP) and palmar abduction of the carpometacarpal (CMC) joint are measured with a goniometer. The first measurement is performed at both sides. ROM is measured from the moment the patient is allowed to move the MCP joint; after 4 weeks of immobilization (when the immobilizing cast is replaced by a removable cast) and at 3, 6, and 12 months.

Kapandji-score is used for assessing the opposition of the CMC joint. The opposition test consists of touching the four long fingers with the tip of the thumb. The more the tip of the thumb is able to oppose to the base of the pink, the higher the score will be. [12] The first measurement is performed at both sides. Kapandji score is measured from the moment the patient is allowed to move the MCP joint after 4 weeks of immobilization (when the immobilizing cast is replaced by a removable cast) and at 3, 6, and 12 months.

Grip strength: measured with a hand-held dynamometer. The measurement includes three trials of maximum grip force using the second handle of a calibrated dynamometer, with the elbow in 90° flexion. Dynamometer settings will be on setting two for all patients. Each center will use the same type of dynamometer. The mean score of three trials will be used for analysis as an absolute measure. Grip strength is measured at 3, 6, and 12 months. The first measurement is performed at both sides.

Pinch strength: key pinch/lateral pinch and tip pinch will be measured. Key pinch includes three trials of maximum force between the radial side of the index finger and the pulp of the thumb, using a calibrated pinch gauge, with the elbow in 90° flexion. Tip pinch includes three trials of maximum force between the tip of the index finger and the tip of the thumb, using a calibrated pinch gauge, with the elbow in 90° flexion. Each center will use the same type of pinch gauge. The mean score of three trials will be used for analysis as an absolute measure. Pinch strength is measured at 3, 6, and 12 months. The first measurement is performed at both sides.

COMPLICATIONS

- Conservative treatment: pressure ulcers, neuropraxia or injury to the sensory superficial branches of radial nerve, arthrosis, chronic instability or limited function.
- Perioperative: vascular damage, nerve or tendon laceration.
- Postoperative: surgical site infection, repeat operation, pressure ulcers, neuropraxia or injury to the sensory superficial branches of radial nerve, arthrosis, chronic instability or limited function.

Peri- and postoperative complications will be recorded according tot the Clavien-Dindo Classification for hand surgery. Repeat operation and subsequent description of the additional treatment method will be reported.

6.2 Randomization, blinding and treatment allocation

All consecutive patients meeting the inclusion criteria will be asked to participate in the study. After the first outpatient clinic visit informed consent will be obtained by the hand surgeon or the investigator of the study site. Computerized randomization will be performed as soon as written informed consent is provided, with Castor EDC. In trials comparing surgery with non-operative management, blinding of patients and surgeons is not possible and therefore randomization of this study is not blinded.

6.3 Study procedures

A detailed description of the procedures is provided under 6.1 Study parameters. A summary of the procedures, including time intervals and standard procedures / procedures for study purposes interval, is provided in Figure 2. below.

Summary study procedures			
Time interval	Description of visit	Measurements	
		Hand function	Questionnaires
Randomization	First OPD visit Handsurgeon confirms diagnosis complete UCL rupture Inclusion & randomization	-	MHQ PSFS EQ-5D short iPCQ
After 4 weeks immobilization/ 4 weeks after surgery	OPD visit, removable cast, refferal to handtherapy	ROM	MHQ PSFS
2 months	-	-	EQ-5D iPCQ, iMCQ
3, 6 and 12 months	OPD visit, evaluation of treatment outcome	ROM Grip and pinch strength	MHQ PSFS EQ-5D iPCQ, iMCQ

ED; emergency department, *OPD*; outpatient department, *UCL*; ulnar collateral ligament, *ROM*; range of motion, *MHQ*; Michigan Hand outcome Questionnaire, *PSFS*; patient specific functional scale, *EQ-5D*; European Quality of Life Five Dimension, *iPCQ*; productivity cost questionnaire, *iMCQ*; medical consumption questionnaire.

Figure 2.

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

6.5 Replacement of individual subjects after withdrawal

Study inclusion continues until 114 participants completed the intervention as well as all assessments.

6.6 Follow-up of subjects withdrawn from treatment

When subjects withdraw from treatment, data of the subject will be used up until the time of withdrawal for analysis, according to the intention-to-treat principle to obtain a complete database of consecutive patients and to avoid attrition bias.

6.7 Premature termination of the study

There will be no early assessment for efficacy or futility. We further assume that both treatment strategies are sufficiently safe. The risk of a surgical procedure in the intervention group is acceptable, considering that each patient in the control group will receive such operation upfront. Hence, we strive for a full completion of the study.

SAFETY REPORTING

6.8 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

6.9 AEs and SAEs

6.9.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure or the intervention, conservative treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

6.9.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgment by the investigator.

An elective hospital admission will not be considered as a serious adverse event. The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

6.10 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

6.11 Data Safety Monitoring Board (DSMB)

Not applicable for this study.

7. STATISTICAL ANALYSIS

Data will be analyzed following intention-to-treat. Categorical variables will be presented as counts and percentages and continuous variables as median and interquartile ranges or mean and standard deviation based on the normality of the data. Differences in characteristics between groups will be compared using Fisher exact and Pearson's χ^2 tests for categorical variables, and Wilcoxon rank sum tests and unpaired t test will be used for continuous variables, where appropriate.

We will conduct a linear regression analysis for longitudinal data (i.e. a mixed model) in which we correct for relevant prognostic factors (age, sex, time between trauma and definite treatment, duration of hand therapy) and baseline scores of the Michigan Hand Questionnaire. In an additional step, we will correct for surgeons depending on the number of treating surgeons as well as the number of patients per treating surgeon. Results will be presented as differences between treatment and control with 95% Confidence intervals. The intervention will be labeled as non-inferior when the non-inferiority margin of 8 lies outside the 95% CI of this difference, regarding the Michigan Hand Questionnaire measured at 6 months as our primary endpoint. In case missing data did not happen randomly, but was related to specific factors (e.g. more missing data for men than for women), we will correct for this. In an additional analysis, the absolute MHQ scores at 6 months will be adjusted for differences in baseline MHQ scores between the intervention and control group. The secondary outcomes: PSFS, EQ5D, ROM, Kapandji score, grip strength, pinch strength and pain will be analyzed in a similar manner. Differences between the two treatment groups in complication rates will be analyzed using the Chi-square test or the Fischer's Exact test (in case the expected incidence was less than five).

In theory, surgery in the intervention arm could result in an unexpectedly suboptimal outcome compared to immediate surgery. To determine whether this is the case, an exploratory analysis will be performed by ranking the changes in MHQ in the entire group of patients who (eventually) underwent surgery and comparing the mean rankings. If the mean ranking of the subgroup that eventually underwent surgery in the intervention arm indicates a suboptimal outcome (mean ranking more than 2 different in the direction of worsening to the detriment of the intervention arm), a critical event committee will be established to assess, based on a relevant extract from the patient file, whether direct surgery would have resulted in a different outcome. To increase the uncertainty for the committee and to avoid assessment bias, several directly operated patients from the control group will also be added to the set to be assessed. The qualitative reporting of the CEC assessment will be of a descriptive nature.

COST EFFECTIVENESS ANALYSIS

This evaluation focuses on the question if the proposed intervention for patients with a complete UCL rupture, including Stener Lesions, using initial nonoperative treatment, is cost-effective compared to operative treatment. The economic evaluation will be performed as a cost-effectiveness (CEA) as well as a cost-utility analysis (CUA) from the societal as well as health care perspectives. [13] The primary economic outcome for the CEA is the costs per unit change in overall hand function and closely relates to the clinical outcome measure. The CEA is performed to enable identification of diagnostic or interventional strategies to be preferred economically in the field of hand surgery. The primary economic outcome for the CUA is the costs per quality adjusted life year (QALY). The CUA is performed to enable priority setting during health care policy making across disease areas and health care settings.

If the null hypothesis in this study of nonoperative treatment not being clinically non-inferior at six months is not rejected, but indeed lower costs are associated with nonoperative treatment, then incremental cost-effectiveness ratios will be calculated as the extra savings per extra unit in MHQ score lost or the extra savings per additional QALY lost. If the null hypothesis is rejected, a costs analysis and an outcome analysis will be done as distinct partial economic evaluations. The time horizon will be 12 months. It is expected that effects and costs beyond 12 months are similar for both treatment strategies and that a lifetime time horizon is redundant.

Differences between groups will be assessed after correction for bias and using accelerate non-parametric bootstrapping to account for sampling variability, generating 5,000 replications. Results will be presented graphically by cost-effectiveness planes. Cost-effectiveness acceptability curves will be drawn for various levels of willingness-to-pay per QALY up to €50,000, because higher levels cannot be justified by the maximum observable disease burden in this target group of patients. A scenario analysis will be applied by excluding the productivity losses following sick leave. Subgroup analyses will be performed for patients with a paid job.

Missing cost and effect data will be imputed using multiple imputation according to the MICE algorithm developed by van Buuren. Rubin’s rules will be used to pool the results from the different multiply imputed databases. [14]

<u>Measurement and valuation of costs</u>

We will gather data on the use of resources and the related costs regarding health care (e.g. medical specialist, hand-physiotherapist, treatment of complications), productivity losses (absenteeism (sick leave) and presenteeism (lowered efficiency while at work due to sick leave from work and lowered productivity while a work)) and out-of-pocket

expenses by patient and family members (e.g. health related travel, extra private help). The Dutch iMTA Medical Consumption Questionnaire and iMTA Productivity Cost Questionnaire will be adapted to and prepared for the current study setting and disseminated to patients for completion after two, three, six and twelve months of follow up.(11,12) Case report forms or electronic patient dossiers will be used to gather in-hospital data. Unit costing will be based on the most recent Dutch guideline on costing in health care research at the time of data analysis. Costing of productivity losses will adhere to the friction costs approach with the current friction period at time of analysis.(13) The base year for costing will be 2022, with unit costs price-indexed if originating from other calendar years.

Patient outcome analysis

Patient outcome analysis in addition to the clinical outcome measures relevant to patients (disability, pain, hand function) the economic evaluation will include the measurement of health status at baseline (within 2 weeks after trauma), at two, three, six and 12 months after injury with the EQ-5D-5L. [15] This questionnaire consists of 5 items, measuring (at 5-point scales) whether patients experience problems, and if so, to what extent with regard to mobility, self-care, daily activities, pain/complaints, and mood. Existing health valuation scoring algorithms (Dutch reference values available through www.euroqol.org) will be used to assign a health utility to each 5-items score pattern. The number of QALYs for each patient will subsequently be calculated by interpolation between successive measurement and determining the area under the curve for the follow-up period of 12 months.

ETHICAL CONSIDERATIONS

7.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki, version 64, October 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO) and the Algemene Verordening Gegevensbescherming (AVG).

7.2 Recruitment and consent

After the diagnosis complete UCL rupture has been confirmed by the hand surgeon and the patient meets the eligibility criteria, the patient will be informed about the study by the hand surgeon. When the patient is open to participation, the patient is informed that the coordinating investigator of the study site will take contact after a period of reflection (days) and when the patient agrees to participate, written informed consent is provided for participating in the study (randomization, treatment, analysis of data, completion of questionnaires, completion of follow-up), to reuse the data and to approach patients for follow-up studies.

7.3 Objection by minors or incapacitated subjects

Not applicable.

7.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor also has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study. An exemption from the obligation to take out a WMO (Medical Research Involving Human Subjects Act) subject insurance has been granted by the Medical Ethics Review Committee (METC) based on Article 7, sixth paragraph, of the WMO. According to the METC, participating subjects face minimal or no risk as two common treatment methods are being compared. The liability insurance has been arranged in accordance with the provisions outlined in Article 7, ninth paragraph, of the WMO.

7.5 Incentives

Subjects will not receive compensation for participation in the study.

8. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

8.1 Handling and storage of data and documents

Castor EDC will be used for storage of raw data and backup. All data is captured in Castor and is pseudonymized in such a way that the personal data can no longer be attributed to a specific data subject without the use of additional information. Such additional information is kept separately and it is subject to technical and organizational measures (e.g. information is not going outside of the study site that is including the patient) to ensure that the personal data are not attributed to an identified or identifiable individual. Additional data stored on the hard disk of IT system of the study site and protected by a password, only accessible by the coordinating investigator of the study site. Local storage of the data after the data collection phase (editing and analysis); csv. files exported from Castor EDC to analyze the data, protocols, contracts, documents and software of data editing are stored on the secure server of the Diakonessenhuis. All data will be retained for a maximum of 15 years (approval of the patient is covered by the patient informed consent form) concerning reproducibility. Depending on the end products in terms of reports and articles, the processed and used data will still be stored per product.

8.2 Monitoring and Quality Assurance

Monitoring will be performed in compliance with Good Clinical Practice (GCP) and rules and regulations as described by the Nederlandse Federatie van Universitair Medische Centra (NFU) in order to achieve high quality research and secure patient safety. Qualified and independent monitors will have access to the data and source documents of the trial.

8.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion. Submission of an amendment includes a covering letter, an extract of the modified document and the new document.

8.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed

the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

8.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC at the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.
Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

8.6 Public disclosure and publication policy

The principal investigator (Mark van Heijl) and coordinating investigator (V.A.P. van de Lücht) are leading authors in this study. All investigators in the participating hospitals will be named collaborator in the assessment of this study. The principal investigator and study designers (further to determine) are allowed to present the results on research conferences.

9. REFERENCES

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