RODEO  Trial

ROutine versus on DEmand removal Of the syndesmotic screw; a randomized controlled trial

PROTOCOL TITLE 'R*outine versus on demand removal of the syndesmotic screw; a randomized controlled trial*'

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AOFAS	**American Orthopedic Foot and Ankle Score**
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**
IB	**Investigator's Brochure**
IC	**Informed Consent**
ISS	**Injury Severity Score**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
OMAS	**Olerud-Molander Score**
POWI	**Postoperative wound infection**
(S)AE	**(Serious) Adverse Event**
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**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Does the syndesmotic screw need to be removed following placement for an ankle fracture? We hypothesize that the outcome in patients with removal on demand is not inferior to the outcome in patients with routine removal. By omitting routine screw removal a reduction in patient morbidity and costs will be achieved.

Objective: To demonstrate that the functional outcome of 'removal on demand' of the syndesmotic screw is non-inferior compared to routine removal of the syndesmotic screw in patients with an ankle fracture or an isolated syndesmotic injury.

Study design: Pragmatic multicenter randomized controlled non-inferiority trial.

Study population: Adult patients with a syndesmotic screw placed for an unstable ankle fracture with concomitant acute syndesmotic injury.

Intervention (if applicable): On demand removal of the syndesmotic screw; i.e. removal is only performed in case of symptomatic hardware such as painful hardware or hardware (supposedly) causing restricted range of motion.

Main study parameters/endpoints: Primary outcome: Functional outcome according to the Olerud-Molander score. Secondary outcomes: Adverse events, ankle function, quality of life, and costs.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Participating in this study does not propose additional risk to the patient compared to current practice. Both treatment strategies are well known and frequently applied. No extra procedures or visits to the outpatient clinic are required when participating in the study.

1. INTRODUCTION AND RATIONALE

Ankle fractures are among the most common fractures. It is estimated that more than 25000 people suffer from an ankle fracture in the Netherlands annually and the incidence is rising[1]. Both young and elderly people are at risk for these fractures. In general younger people are more at risk as a result of a more active lifestyle and elderly people because of poorer bone quality[2,3]. Approximately half of the patients with an ankle fracture require surgical treatment because of joint instability. In approximately 20% of these fractures there is a concomitant injury of the syndesmosis and syndesmotic repair is indicated[4]. A syndesmotic 'positioning screw' is placed through the fibula into the tibia to assure stability and allow the syndesmotic ligaments to heal. Elaborate research has been conducted regarding the technical aspects of the placement of the syndesmotic screw. For example, the number of required screws, its diameter, level of placement and whether it should engage three or four cortices has been investigated thoroughly[5–9]. After a period of 8 – 10 weeks the syndesmosis will generally be healed and the screw will lose its function. It is an ongoing discussion whether the syndesmotic screw needs to be removed subsequently. Most surgeons advocate its removal because of suspected impaired range of motion and chance of breakage of the screw[8,10–12]. During normal ambulation the fibula moves and the syndesmosis widens[13,14]. The positioning screw is thought to restrict this movement and the screw is therefore removed after 8 – 12 weeks. However, several case series have shown similar outcomes in patients in which the syndesmotic screw was retained compared to patient in whom the syndesmotic screw was removed[15–17]. The positioning screw is most likely not causing complaints in patients with retained screws because of loosening or breakage of the screw[18–20]. In the Netherlands both routine removal and removal on demand of the syndesmotic screw are well accepted treatments. In a new national clinical guideline on ankle fractures, routine removal of the syndesmotic screw is not advocated anymore and both treatments are recognized as regular treatment. Standard treatment differs between hospitals but also between physicians. This inter-physician treatment variation is also demonstrated in a national survey by Schepers et al.[8].

Currently there is not enough evidence for neither routine removal or removal on demand, providing such evidence is desirable for both physicians and patients.

2. OBJECTIVES

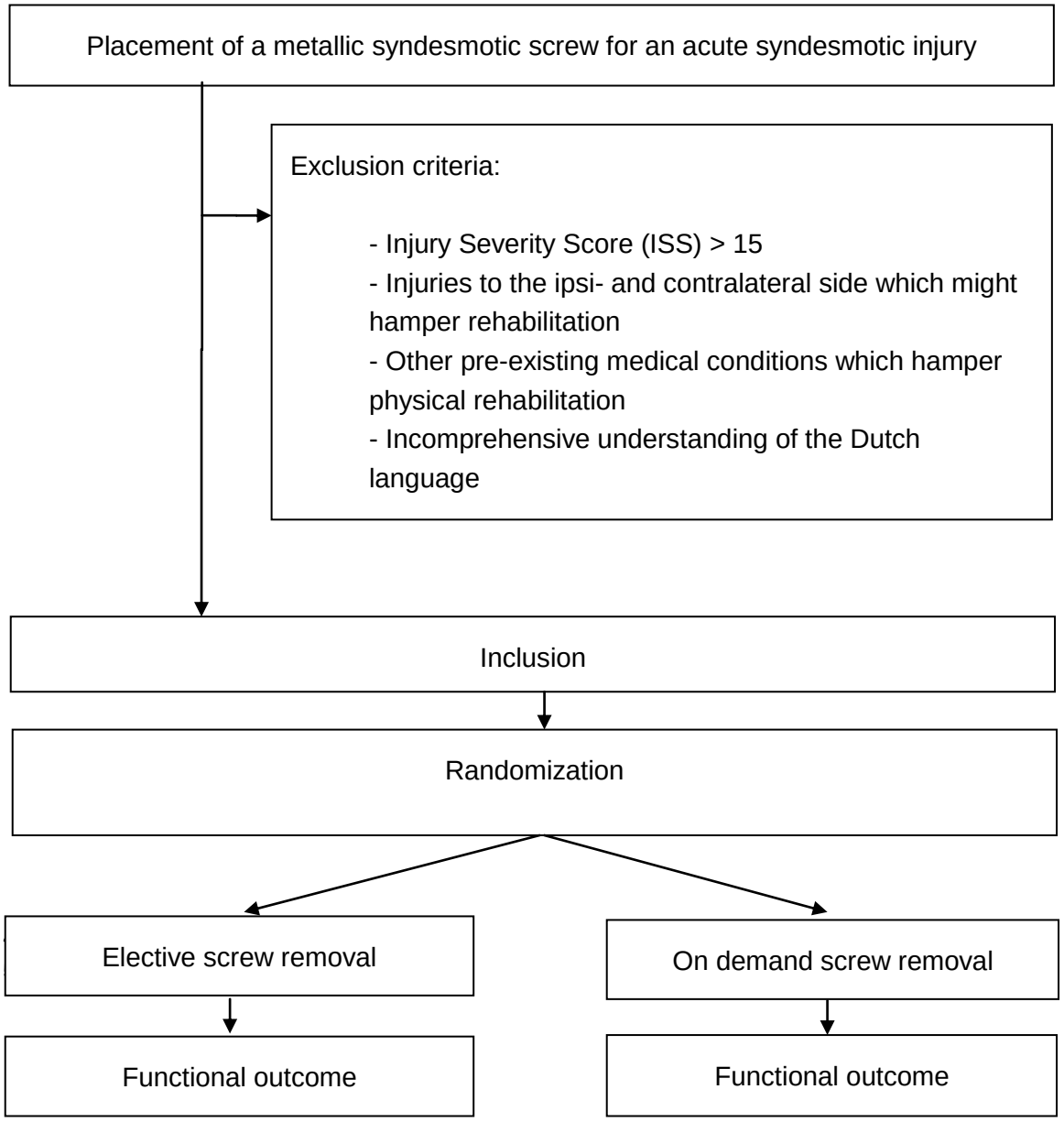
Primary Objective: To demonstrate that an on demand removal strategy of the syndesmotic positioning screw is non-inferior in functional outcome compared with routine removal of the syndesmotic positioning screw.

Secondary Objective(s): We aim to compare ankle function and amount of adverse events between the two treatment strategies. We also intent to investigate the quality of life and economic impact of both routine removal and removal on demand.

3. STUDY DESIGN

The study will be a pragmatic, multicenter randomized controlled non-inferiority trial. The study will compare a removal on demand strategy with a routine removal strategy regarding the syndesmotic screw. We will advocate a preferred method of fixating, based on current literature, of the syndesmosis (i.e. a single 3,5 mm metal screw through 3 cortices). However, the pragmatic design implies that the final decision technical details regarding the placement of the screw (e.g. number of screw(s), size of the screw(s) and number of cortices engaged) are left at the discretion of the operating surgeon. In total the duration of the study will be three years. Inclusion will take approximately two years and the follow-up lasts one year. An overview of the study is shown in Figure 1.

Figure 1. Flow chart of the study design.



4. STUDY POPULATION

4.1 Population (base)

The study population will consist of patients >17 years of all sexes and ethnicities with an ankle fracture and concomitant syndesmotic injury requiring stabilization, operated within two weeks of trauma.

4.2 Inclusion criteria

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

- Over 17 years of age
- Placement of a metallic syndesmotic screw for an unstable ankle fracture or an isolated syndesmotic injury
- Syndesmotic screw placed within two weeks of the trauma
- Being in such condition that one is able to possibly undergo a second procedure

4.3 Exclusion criteria

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

- ISS score >15
- Injuries to the ipsi- and contralateral side which might hamper rehabilitation
- Other medical conditions which hamper physical rehabilitation
- Incomprehensive understanding of the Dutch language

4.4 Sample size calculation

We based our sample size calculation on a non-inferiority design. The Olerud-Molander score (OMAS) will serve as primary outcome measure. We have used the results from an earlier study on this subject for our sample size calculation[21]. For the sample size calculation we hypothesized an equal OMAS between the two groups. Using a one-sided significance level (a) of 0.025 and a power (ß) of 90% with a standard deviation (s) of 19 points (derived from the study mentioned before) and setting our non-inferiority limit at 10 a total of 76 patients are needed in each study arm. Taking a 10% loss to follow-up into account, a total number of 167 subjects will be needed to demonstrate non-inferiority between the two treatment strategies. We chose our non-inferiority limit because of the nature of the OMAS. For the different domains on the OMAS 0, 5 or 10 points can be awarded. In our opinion one of the two treatments has to score lower at least in two domains (or two categories within one domain) to be non-inferior. This automatically leads to an difference of at least 10 points on the OMAS. Furthermore we performed a sample size calculation for a subgroup analysis (i.e. patients younger than 60 years and over 60

years). We hypothesize that the SD will be lower in these subgroups due to increased homogeneity, therefore we have used an SD of 16 for the sample size calculation of the subgroups. Using a significance level (a) of 0.05 and a power (ß) of 90% 88 patients are needed in each subgroup to prove non-inferiority. Taking 10% loss to follow-up into account a total of 193 patients will be randomized.

5. TREATMENT OF SUBJECTS

Patients allocated to the intervention group will not undergo scheduled removal of the syndesmotic screw. They will be allowed to start weight bearing according to the preference of the treating surgeon. The screw will only be removed in case of symptomatic hardware, defined as: 1) hardware causing pain, 2) hardware (suspected of) causing restricted range-of-motion 3) explicit request of the patient 4) an infection or 5) other problems related to the screw such as protruding screws. As stated before the screw will only be removed after a consultation of the treating surgeon (except in patients who wish to no longer participate in the study). Patients in the routine removal group will undergo routine removal of the syndesmotic screw 8 – 12 weeks post-operatively (according to the preference of the treating surgeon). Patients will not undergo routine removal in case of 1) a contra-indication for undergoing a second procedure for example due to a (new) medical condition or 2) explicit request of the patient after consultation of their treating surgeon.

6. INVESTIGATIONAL PRODUCT

The RODEO-trial does not investigate a product. All products are already used in daily surgical practice. Therefore this chapter is not applicable.

7. NON-INVESTIGATIONAL PRODUCT

The RODEO-trial does not investigate a product. All products are already used in daily surgical practice. Therefore this chapter is not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary outcome parameter will be functional outcome measured through the Olerud-Molander ankle score (OMAS). The OMAS is specially developed for the assessment of ankle function following an ankle fracture[22] and is the most widely used score system in reports on ankle fractures[6,20,23]. Furthermore has it a close relation with function recovery and quality of life and has been validated as such[20]. The OMAS has nine items on which patients are assessed. A maximum of 100 points can be acquired which resembles full ankle function. Zero points resemble complete loss of ankle function. We will insert anchor-based questions in the OMAS in order to be able to define a minimum clinical important difference (MCID) as described by Walenkamp et al[24].

8.1.2 Secondary study parameters/endpoints (if applicable)

- Functional outcome through the American Orthopedic Foot and Ankle Score (AOFAS)
- Pain though the Visual analog scale (VAS-score)
- Range-of-motion
- Postoperative wound infections
- Recurrent syndesmotic diastasis
- Implant failure (breakage of the screw)
- Synostosis
- Quality of life though the EQ-5D-5L
- Health care consumption through the iMCQ
- Loss of productivity through the iPCQ

8.1.3 Other study parameters (if applicable)

- Gender
- Age
- Body Mass Index (BMI)
- Co-morbidities
- Medical history
- American Society of Anesthesiologist (ASA)- classification
- Substance abuse
- Bone mineral density (BMD)
- Fracture characteristics
- Surgical characteristics
- Duration of non-weight-bearing period
- Use of physiotherapy

8.2 Randomization, blinding and treatment allocation

Patients will be randomly assigned in a 1:1 allocation ratio to one of the following study arms:

1: Routine removal of the syndesmotic screw 8 – 12 weeks following the index procedure

2: Removal on demand of the syndesmotic screw

Randomization will be stratified by center and by age (i.e ≥ 60 years and < 60 years).~~.~~ Randomization will be blocked within strata. Randomization sequence is generated by a dedicated computer randomization software program, ensuring allocation concealment. Randomization will mostly be performed ~~at the outpatient clinic~~ by ~~treating physician using~~the coordinating investigator using a dedicated, password protected, SSL–encrypted website. ~~In some cases the coordinating investigator may randomize for the treating surgeon.~~

8.3 Study procedures

Study procedures are shown in Figure 2.
Patients will be informed about the study by their treating physician following the procedure in which the syndesmotic screw was placed. After this, patients are contacted by the coordinating investigator to request participation in the study. In case a patient wishes to participate in the study, ~~the treating physician is contacted~~ and when signed informed consent has been obtained the patient will be randomized. The ~~whole~~ informed consent procedure and randomization will be ~~conducted~~performed by the coordinating investigator. The coordinating investigator will check the in- and exclusion criteria ~~by~~with the patient and ~~by~~ the treating physician. After randomization the treating physician is ~~Syndesmotic~~contacted to inform her/him about the result of the randomization. Syndesmotic screw removal is subsequently planned (or not) according to randomization 8 – 12 weeks following placement of the syndesmotic screw. Three months postoperatively the index procedure patients are assessed at the outpatient clinic. Patients are instructed to visit the outpatient clinic sooner in case of any signs of a POWI: warmth, redness, pain, drainage or a fever above 38.5 degrees Celsius. During the visit to the outpatient clinic the patient is seen by his/her treating physician and the coordinating investigator. The coordinating investigator will document signs of a POWI and will determine its presence or any special findings on physical examination. Furthermore patients are requested to fill in several questionnaires. The questionnaires will be send digitally ~~due the~~ usinge ~~of~~ Castor,if a patient ~~didn't~~does not have an e-mail address, ~~easily~~daily ~~-~~access to the internet or at patients preference the questionnaires will be filled outin ~~on~~at the outpatient clinic or will be send to their home address (Appendix F1-1, F1-2, F1-3, F1-4 and F1-5). At the 6 and 12 months follow-up patients are requested to fill in the same questionnaires and the range-of-

motion is measured by the coordinator investigator who will perform the follow-up assessments on site. Follow-up will take place within a window of 2 weeks of the projected follow-up moment.

Figure 2: Overview of the RODEO-trial

RODEO-trial	**Enrollment**	**Randomization / Allocation**	**Follow-up**		
TIMEPOINT	Post-operatively	8 – 12 weeks post-operatively	3 months Post-operatively *	6 months Post-operatively *	12 months Post-operatively *
Enrollment					
Eligibility screen	X				
Informed Consent	X				
Intervention					
Removal of syndesmotic screw (according to randomization)		X			
Assessment					
Plain radiographs	X		X		X
OMAS			X	X	X
Visual analogue pain scale (VAS)			X	X	X
Range-of-Motion				X	X
POWI			X		
AOFAS			X	X	X
EQ-5D-5L			X	X	X
i-MCQ			X	X	X
i-PCQ			X	X	X

*: months following the index procedure.

8.4 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.

8.4.1 Specific criteria for withdrawal (if applicable)

None

8.5 Replacement of individual subjects after withdrawal

Individuals who withdraw from the study will not be replaced by new subjects unless the drop-out exceeds the anticipated drop-out of 10%.

8.6 Follow-up of subjects withdrawn from treatment

Individuals who withdraw from treatment will be followed using the study follow-up schedule.

8.7 Premature termination of the study

This study will be terminated prematurely if and when patients experience an amount of discomfort or adverse events that is disproportionate to the benefit of the study and presents too great a risk for the participating study subjects.
In case the study is ended prematurely, the coordinating PI will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

9. SAFETY REPORTING

9.1 Section 10 WMO event

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 jeopardise 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.

9.2 AEs and SAEs

9.2.1 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 experimental intervention. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.
The medical assessment of severity will be determined by the investigator. The severity will then be graded according to the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research patient.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

For this study loss of reduction and POWI managed with oral antibiotics are important AE's and will be in reported in the CRF.

The investigator will appreciate the severity of an event and give his opinion on whether the event is related or not to the study procedures. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural

history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the study procedure will be considered and investigated.

9.2.2 Serious adverse events (SAEs)

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

- 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;~~
- is a congenital anomaly or birth defect
- ~~is a congenital anomaly or birth defect;~~
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

NOTE: The following types of (prolongation of) hospitalisation are not considered to be a SAE:

- Any admission unrelated to an AE, e.g., for labour/delivery, cosmetic surgery, social and/or convenience admissions to a hospital;
- Protocol-specified admission, e.g., for a procedure required by the study protocol;
- Admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) **and** has not increased in severity or frequency as judged by the clinical investigator.

In case of an serious adverse event the main investigator from a participating center needs to contact the coordinating investigator within three days.
The coordinating investigator will dived the SAE's into two groups.

SAE's which are related to this study e.g. hospitalization due to wound infection (which have to be treated with intra venous antibiotics) or loss of reduction which needed a revision.

SAE's which have no relation to this study.

The sponsor (coordinating investigator) will report the SAEs which are related to this study through the web portal *ToetsingOnline* to the accredited METC that approved

the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events.
The remaining SAE's will be listed in an overview list that will be submitted once a year to the METC.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event. This is for a preliminary report with another 8 days for completion of the report.

9.3 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

9.4 [Data Safety Monitoring Board (DSMB)

This study is considered a low risk trial, since both treatments are well-known and part of standard daily care. Therefore, ongoing safety surveillance and interim safety analyses by a Data Safety Monitoring Board (DSMB)/Safety Committee is deemed not necessary.

9.5 Study monitoring

This chapter is not applicable. ~~The study will be monitored in all centerasopenthe study does not investigate a drugmedication involved.s. All monitoring visitations will be scheduled at mutually agreeable times, periodically during the study at frequency deemed appropriate. These visits will be conducted to evaluate the progress of the study, to ensure that the rights and well-being of the subjects are protected, to check that the reported clinical study data are accurate, complete and verifiable from source documents, and if the conduct of the study is in compliance with the approved protocol and amendments, good clinical practice and applicable national regulatory requirements. A monitoring visitation will include a review of the essential clinical study documents (regulatory documents, case report forms, source documents, subject informed consent forms, etc.) as well as discussion on the conduct of the study with the investigators. The investigators should be available during these visitations to facilitate the review of the~~

~~clinical study records and to discuss, resolve and document any discrepancies found during the visitation.~~

10. STATISTICAL ANALYSIS

Data will be analyzed according to the intention-to-treat and the per-protocol principle. Descriptive methods will be used to assess quality of data, homogeneity of treatment groups and endpoints. Normality of the data will be analyzed by visually inspecting the histograms. Secondary outcomes will be analyzed using either a t-test or Mann-Whitney U test for continuous data according to the distributing of the data and a Chi Square test for categorical data. Missing data will be handled through multiple imputation with predictive mean matching.

10.1 Primary study parameter(s)

The primary analysis will focus on the functional outcome after 12 months. The two groups will be assessed on a per-protocol base using an unpaired one sided t-test or Mann-Whitney U test in case of non-normality. Additionally the primary outcome will be analyzed using multivariate logistic regression, adjusting for the stratifying variable. The mean difference in the primary outcome between the two groups will be presented together with the lower bound of the 95% confidence interval. If, the lower bound of the 95% confidence interval is higher/less negative than -10 OMAS point difference and the 95% confidence interval does not include this non-inferiority limit in both the intention to treat and per protocol analysis, non-inferiority is considered proven.

10.2 Secondary study parameter(s)

Differences in the secondary outcome parameters between both treatment groups will be analyzed using the two groups Student's t-test, Mann-Whitney U test, Chi-square test or Fisher's exact test when appropriate. In addition, multivariate logistic regression analysis for binary outcomes and linear regression analyses for continuous outcomes will be performed adjusting the stratifying variable.

10.3 Other study parameters

Descriptive analyses will be performed for patient, fracture and surgical characteristics, using means and standard deviations, medians and interquartile ranges or counts and percentages, when appropriate. Differences between groups will be assessed using the two groups Student's t-test, Mann-Whitney U-test, Chi-square test or Fisher's exact test when appropriate.

10.4 Interim analysis (if applicable)

Both investigated treatments are considered standard care and therefore this is a low risk study. For this reason a DSMB board and an interim analysis are deemed not necessary.

10.5 Economic analysis

10.5.1 General considerations

We hypothesize that retaining the syndesmotic screw is non inferior to routine removal for the outcome of functional recovery and quality of life. The economic evaluation of retaining the syndesmotic screw against routine removal of the syndesmotic screw will be performed as cost-utility analyses and a cost effectiveness analysis from a societal perspective with the costs per quality adjusted life year (QALY) and the costs per point functional recovery improvement as the primary economic outcomes. The cost-utility analysis allows for priority setting during health care policy making across patient populations, interventions and health care settings. The cost-effectiveness analysis (CEA) closely relates to the clinical outcome parameter and may be used for prioritization or bench marking of strategies that enhance surgical patient safety. A life-time horizon is recommended by the guideline. Strictly, we cannot rule out that there may be some consequences of not removing the screw on the long term (10-20 years) – e.g. reduced functioning, bone density, etc. However, evidence on such long term outcomes is currently lacking, and through discounting these consequences will hardly affect the economic analyses. We therefore will base the CEA and CUA on a time horizon of 12 months, because we expect relevant differences in health outcome and costs to be present in the first 12 months after the placement of the screw; and will recommend further research on long term outcomes to generate such evidence in patients where the syndesmotic screw is not removed. For this time horizon no discounting of effects and costs will be needed. Incremental cost-effectiveness ratios will be calculated as the difference in costs per QALY gained and as the difference in costs per additional point of improvement in functional recovery. Sampling variability will be accounted for by bias-corrected and accelerated non-parametric bootstrapping. Results will be reported along with their 95% confidence intervals and displayed graphically with cost-effectiveness planes and with cost-effectiveness acceptability curves for societal willingness-to-pay levels to 30,000 euros. with a post-operative wound infection after surgical removal against retaining the screw. Some missing data can be expected, if missing data is at random this will be handled through multiple imputations with predictive mean matching up. One-way and multi-way sensitivity analyses will be done for the unit costs of the surgery in which the syndesmotic screw is removed and for international differences in

utility weights (see below). Considering that the functional recovery may differ by between patient groups, subgroup analyses will be done for (i) elderly and young patients, (ii) patients.

10.6 Cost analysis

Medical, patient and productivity costs will be included in the evaluation. The medical costs cover the costs of surgery, anesthesia, theater, peri-operative materials, inpatient stay at the ICU and the wards, diagnostic and therapeutic (other than surgical) procedures, medication against infections. Patient costs include out-of-pocket expenses, including over-the-counter medication and health care related travel. Productivity costs reflect losses of productivity resulting from being absent and decreased productivity during work. Hospital health care utilization will be retrieved from case report forms (CRF) and hospital information systems. Data on out-of-hospital health care will be gathered with the iMTA Medical Consumption Questionnaire (iMCQ) adjusted to the study setting. The absence from work and impact on work productivity will be documented with the iMTA Productivity Cost Questionnaire (iPCQ). Questions on out-of-pocket expenses will be added to these patient questionnaires. Patients will be asked to fill in questionnaires 3, 6 and 12 months after initial surgery with placement of the syndesmotic screw. Unit costing of health care resources will be derived from the most recent national health care costing guideline for economic evaluations at the time of analysis. Market prices will be used for medications. Productivity losses will be based on the friction cost method (with general as well as age- and sex-specific unit costs per hour of productivity loss). If necessary costs will be price indexed based on consumer price indices(CPI). Costs will be calculated for individual patients as the product sum of the resource use and the respective unit costs.

10.7 Patient outcome analysis

Patients will be asked to complete the Olerud Molander Score (OMAS) and American College of Foot and Ankle Surgeons score (AOFAS) and the EQ-5D-5L health status questionnaire at 3, 6 and 12 months after initial surgery. These questionnaires will be included in the CRFs. The EQ-5D-5L scoring profiles can be converted into a health utility score based on general population based Dutch tariffs. The UK tariffs will be applied as a sensitivity analysis QALYs will be calculated for each patient after linear interpolation between the successive health utility assessment over time. The budget impact of retaining the syndesmotic screw will be assessed from governmental and insurer perspectives in accordance with the ISPOR guidelines. The governmental perspective will be from both the broad societal perspective as well as the budgetary health care framework (BKZ) and can be used to help setting priorities in health care optimization.

The insurers perspective can be used to examine the net financial consequences of leaving the syndesmotic screw in place instead of removing it in a second operation.

10.8 Budget impact analysis

The budget impact analyses can be used to guide reimbursement decisions and price and volume negotiations between insurer and health care provider. The budget impact study will be prevalence based, reflecting the net savings of foregoing the second operation in which the screw is removed. The time horizon of the budget impact is 4 years, starting in 2021. Several scenarios will be examined , full implementation, partial implementation (50%, 75%) and gradual implementation over the years. Sensitivity analyses will be performed for the percentage of patients in which the screw has to be removed due to hardware related complaints and the number of post-operative wound infections after the second operation in which the screw is removed. For the budget impact analysis from a governmental societal perspective the most recent guidelines for (unit) costing in health care research will be applied. In case of impact assessments concerning premium financed health care and from the insurer perspective, existing tariffs at the time of analysis will be used (DBC costing).

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted in accordance with the principles of the Declaration of Helsinki (64th version, October 2013) and according to the laws governing human research in the Netherlands (Wet Medisch-wetenschappelijk Onderzoek met mensen – WMO and Best Clinical Practice (BCP)) and the guidelines of the Central Committee for Research involving Human Subjects (Centrale Comissie Mensgebonden Onderzoek - CCMO). Therefore, this studywill be suspected to examination of the Medical Ethical Committees of all participating hospitals and approval will be obtained before start of the study. Written informed consent will be obtained from patients before inclusion in the trial.

11.2 Recruitment and consent

The patient will be informed about the RODEO-trial following surgery when a syndesmotic screw is placed or when he or she visits the outpatient clinic following surgery by his or her treating physician. Documents are handed to the patient and the patient is asked to read the patient information letter (Appendix E1). Patients will have a minimum of three days to decide whether they want to participate or not in the study. For patients recruited directly postoperatively this means they can be included upon their first visit at the outpatient clinic. For patients who are informed for the first time at the outpatient clinic the coordinating investigator will contact them by phone (if the patient agrees to be contacted by phone by the coordinating investigator). Randomization will take place after they have returned the informed consent forms.

11.3 Objection by minors or incapacitated subjects (if applicable)

Minors and incapacitated patients will not be included in this study.

11.4 Benefits and risks assessment, group relatedness

A recent systematic review suggests that our intervention is safe and has similar functional outcome compared to the routine removal[25]. Subjects will not undergo additional investigations and interventions due to participation in the RODEO-trial and therefore risks to subjects involved in this trial are at least similar to current practice. Potential benefits for subjects in the investigational treatment arm could be a lower risk of surgical site infections and not having to undergo a secondary procedure.

11.5 Compensation for injury

The sponsor has a liability insurance which is in accordance with article 7, subsection 6 of the WMO. In a survey conducted by Schepers et al. 20 % of all surgeons stated they do not routinely remove syndesmotic screws[8]. Furthermore a national clinical guideline on ankle fractures is to be released in December this year (one of the applicants, dr. T. Schepers, is a member of the guideline committee). In this guideline routine removal of the syndesmotic screw is not mandatory and both treatments (routine removal and removal on demand) are considered part of regular practice. Therefore additional insurance is deemed not necessary.

11.6 Incentives (if applicable)

Subjects will not receive special incentives, compensation or treatment through participation in the study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Patients will be coded by a numeric randomization code (anonymized) and the principal investigator and study coordinators will be the only one with access to it. The source data will be stored digitally and will be kept by the project leader for 15 years after the inclusion of the last patient.

12.2 Monitoring and Quality Assurance

The study will be monitored by the Clinical Research Unit according to ICH-GCP guidelines throughout its duration by (a) BROK or GCP-certified monitor(s) according to the Monitoring Plan (Appendix F4). The assigned monitor is not involved in the clinical trial as part of the trial site staff. The monitor's qualifications, including the received GCP-training, are documented.

12.3 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.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 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.

12.5 End of study report

The investigator will notify the accredited METC of 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.

In case the study is ended prematurely, the investigator 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.

12.6 Public disclosure and publication policy

The trial will be registered within the Clinicaltrials.gov trial register after inclusion of the first patient. The study protocol will be published in a peer-reviewed open access medical journal. The results of the RODEO-trial will be submitted to a peer-reviewed medical journal regardless of the study outcomes. Co-authorships will be based on the international guidelines of the international committee of medical journal editors (ICMJE). There is a minimum of 20 randomized patients to obtain 1 co-authorship. Per site it is internally determined which local investigator will be co-author. The study coordinator will be first author on the primary and subsequent manuscripts. Third, penultimate and last authorships are for the principal investigators and project leaders of the manuscript. All other authors will be listed in alphabetical order. Clinicians who are involved in this study and do not fulfil the previously mentioned criteria, will be noted as ‘collaborator’ in the final manuscript and the medical journal will be asked to present the names of all collaborators and to be listed as well in PubMed. For purposes of abstract presentation and publication, any secondary publication will be discussed with all local participating principal authors.

13. STRUCTURED RISK ANALYSIS

The RODEO-trial does not investigate a product, therefore this chapter is not applicable

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