How should we treat a patient with a distal radius fracture after closed reduction? A cluster RCT

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PROTOCOL TITLE '*How should we treat a patient with a distal radius fracture after closed reduction? A cluster RCT*'

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Laboratory sites	***NA***
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TABLE OF CONTENTS

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

SUMMARY

Rationale: Distal radius fractures (DRF) are the most common fractures in the adult population. There is no consensus on conservative treatment of a displaced DRF.
Objective: To evaluate the cost-effectiveness of treatment with a circumferential cast compared to treatment with a splint, in patients with a reduced distal radius fracture. The hypothesis is that reduced distal radius fractures treated with a circumferential cast instead of a splint, results in less fracture re-displacement, fewer surgical interventions, less complications and lower costs.
Study design: Cluster randomized design, randomization will take place on hospital level. All patients will be followed for 1 year.
Study population: Adult patients with a primary displaced fracture of the distal radius which is treated conservatively after closed reduction.
Intervention (if applicable): In one group the fracture will be initially immobilized with circumferential below-elbow cast, and in the other group the fracture will be initially immobilized with below-elbow splint.
Main study parameters/endpoints: Difference between groups in proportion of fracture re-displacement of the initial reduced distal radius fracture. Besides, differences in medical consumption, absence from work or decreased productivity, and patient costs, will be assessed.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden is primarily time (visit of outpatient clinic, and to fill in questionnaires). There is no direct benefit from participation or group relatedness.

1. INTRODUCTION AND RATIONALE

Distal radius fractures (DRF) are the most common fractures in the adult population and account for up to 20% of all fractures, which results in an incidence of approximately 33.000 patients per year in the Netherlands (1, 2). Approximately two thirds of DRFs are displaced and require reduction (3). Displaced DRFs are generally reduced in the emergency room and immobilized in either a non-circular splint or a circumferential cast. These reduced fractures are rather unstable which results in fracture re-displacement in 36% of patients (4). Whereas re-displacement of DRFs was previously accepted or reduced in a second attempt (5), nowadays these re-displaced fractures are generally operated on (6). In a search to prevent re-displacement of DRFs and following surgery, our research group recently did a survey among all Dutch hospitals which showed that reduced DRFs are immobilized in a splint in 69% and in a circumferential cast in 31%. Besides, our analysis of 544 patients with reduced DRFs in four different hospitals, showed that re-displacement of DRFs occurred in 10% in circumferential cast and in 20% in a splint. With the current study we aim to minimize re-displacement of reduced DRFs which consequently results in less surgery with fewer complications and less costs. The purpose is to answer the following question: Does primary application of a circumferential cast instead of a splint in reduced DRFs result in fewer re-displacement followed by fewer operations and less cost?

HEALTH CARE EFFICIENCY PROBLEM

Although DRFs are already one of the most common fractures, the incidence will further increase because of the ageing population, increasing life expectancy, and less budget for nursing homes with consequently more falls at home. Our analysis among Dutch hospitals showed that displaced distal radius fractures are generally reduced and immobilized in either a splint or a cast while 10% more fracture re-displacement was seen in a splint. If re-displacement occurs, the fracture is often stabilized with open reduction and internal fixation which results in 9-32% unsatisfactory outcomes and 17% complications (4). By preventing fracture re-displacement a cost reduction of €5567 could be achieved per person, because a distal radius fracture treated in cast costs €506 while surgery costs €6073 (7). In conclusion, health care could become more efficient if we are able to confirm that a cast instead of a splint reduces fracture re-displacement, surgery, complications and costs.

USUAL CARE

Patients who sustain a distal radius fracture which is displaced, are primarily treated in an emergency department. Because the clinical appearance of a displaced radius fracture is distinctive, radiographs are made to demonstrate the type of fracture and its displacement.

Usually, a hematoma block or a procedural sedation and analgesia (PSA) is used as analgesic technique to allow painless reduction of the displaced fracture. The clinician reduces the displaced fracture by either traction with Chinese finger traps and/or a manual reduction manoeuvre. If the fracture is clinically well aligned, the lower arm is immobilized in cast to stabilize the potential instable fracture. Which type of cast is used (circumferential or a splint) differs per hospital. After approximately one to two weeks the patient is invited in the plaster room. If the fracture is stabilized in a splint, either the splint is replaced by a circumferential cast or made circumferential by replacing the elastic bandage with cast . Especially the replacement of the splint for a circumferential cast may cause re-displacement of the fracture. If the fracture is primarily immobilized in a circumferential cast, the cast is checked and adjusted or replaced if necessary. After adjustment of the cast, new radiographs are made to demonstrate the alignment of the fracture. In case of severe displacement, as defined by the guideline distal radius fractures, surgical stabilization of the fracture with a volar plate osteosynthesis is often the first choice of treatment in fit patients.

(SUB)-GROUP OF PATIENTS

The incidence of distal radius fractures is approximately 33.000 patients per year in the Netherlands and occurs most commonly in young males and older females (2). Patients with a distal radius fracture are treated in almost every hospital on daily basis while the treatment among these hospitals is not uniform.

THE INTERVENTION TO BE INVESTIGATED

After reduction of a displaced distal radius fractures (DRF), a circumferential cast is applied to immobilize the fracture and to prevent re-displacement. The clinical and radiological follow-up is the same as the patients treated with a splint except that the cast is left in place till the fracture is healed.

EXISTING EVIDENCE OF EFFECTIVENESS

There is no consensus on conservative treatment of DRFs. Both the Dutch guideline "distal radius fractures"(8) and a Cochrane review (9) report that there is insufficient evidence from randomized trials to determine which method of conservative treatment is the most appropriate for DRFs. One randomized study with only 72 patients that compared cast with a splint, showed a significant better position of the fracture in the group treated with cast (10). Another underpowered randomized study showed no significant differences but had a low follow-up rate of 61%, and selection bias because of treatment choice was based on subjective findings (11). One prospective non-randomized study which only included Colles' fractures compared 5 different types of cast and showed no differences between the small

groups (5). Our large study in 544 patients in 4 Dutch hospitals showed 10% difference in re-displacement in favor of cast in rather stable extra-articular fractures. We expect a higher percentage of re-displacement in our present study because we will also include the more unstable displaced intra-articular fractures. Finally, there is no data available regarding to cost-effectiveness.

GUIDELINE

The Dutch guideline for the treatment of DRFs (8) concluded that the literature is inconclusive and encourages new studies to unravel which type of cast should be used in the treatment of DRFs.

RELEVANCE FOR PRACTICE

DRFs are the most common fractures in the adult population and account for up to 20% of all fractures, which results in an incidence of approximately 33.000 patients per year in the Netherlands (2). The combination of a high incidence of DRFs and expensive surgery makes it a major public health problem. In our recently finished retrospective study of stable extra-articular fractures we found 10% less re-displacement within one week in patients who were immobilized in cast compared to patients immobilized in a splint (unpublished data). We used the definition of displacement as defined in the Dutch guideline. Because our proposed study will also include less stable intra-articular fractures and will have a longer follow-up, we expect a larger difference. This will result in a reduction of surgery with accompanying complications and reduced national healthcare costs. In June 2018 the Dutch Orthopedic Association (NOV) updated the research topics with a high relevance for clinical practice (Agenda Zorgevaluatie Orthopedie 2.0) and the current proposal is included in the newest research agenda and received the highest priority of all upper-extremity and trauma topics. The topics were prioritized by a panel of patients, orthopedic surgeons and health insurance companies, initiated by the Dutch Orthopedic Association (NOV) and Knowledge Institute of Medical Specialists. Thereby, we received written support from the Dutch Trauma Association (NVT), the Dutch Orthopedic Association for Traumatology (NVOT), the Dutch association for Emergency Department Consultants (NVSHA) and the Dutch Association for Hand surgery (NVvH).

PATIENT PARTICIPATION

According to the Dutch patient federation and our own investigation, there is no specific patient organization for patients with DRFs. In absence of an adequate patient association, we formed a panel of patients who were treated for a displaced distal radius fracture to think

along with and comment on our study. The patient panel provided feedback on the relevance and the outcome of the study.

ANTICIPATED COST-EFFECTIVENESS

In our recently finished retrospective study of stable extra-articular fractures we found 10% less re-displacement in cast within one week which resulted in less surgical procedures. Patients treated with circular cast have minimally equal functional outcome (Quick-DASH) after 6 months, but with less complications and lower costs. The costs of conservative treatment with splint or cast are €506, while surgery of a secondary displaced fracture costs €6073. Although we expect a larger difference of secondary displacement because of inclusion of intra-articular fractures and longer follow-up, 10% difference will already result in a yearly anticipated cost-effectiveness of €12.800.000 (7). Thereby we did not take the higher rate of complications and extra work-related costs in account. Both interventions are financially compensated by the health insurance in the Netherlands.

IMPLEMENTABILITY

Aim is to implement the results of this study in the next update of the Dutch Distal Radius Fracture guideline. The results will be presented to different professional associations of orthopaedic surgeons, trauma surgeons, emergency physicians and on several (inter)national scientific conferences. They also will be published in international peer-review journals. For patients, the intervention should enhance their quality of life by sparing them (the complications associated with) a surgical procedure. Finally, the cost effectiveness of the intervention will make it of interest to health authorities and insurance companies.

DIVERSITY

The study will be conducted in one University Medical Center and 9 teaching hospitals in order to form a study population that reflects the Dutch patient population. We expect a good collaboration with these hospitals due to our previous experiences with the study '*Should a patient with a suspected scaphoid fracture be treated with cast? An RCT*' which is supported by ZonMw (project number: 843002802).

2. OBJECTIVES

The aim of the present proposal is to evaluate the cost-effectiveness of treatment with a circumferential cast compared to treatment with a splint, in patients with a reduced distal radius fracture.

HYPOTHESIS

The hypothesis is that reduced distal radius fractures treated with a circumferential cast instead of a splint, results in less fracture re-displacement, fewer surgical interventions, less complications and lower costs.

RESEARCH QUESTION

Primary objective

To assess whether treating patients with a reduced distal radius fracture with a circumferential cast instead of a splint, results in less fracture re-displacement.

Secondary objective

To assess whether treating patients with a reduced distal radius fracture with a circumferential cast instead of a splint, results in fewer surgical interventions.

To assess whether treatment of patients with a reduced distal radius fracture with a circumferential cast is cost-effective compared to treatment with a splint.

3. STUDY DESIGN

The present study compares the cost-effectiveness of two treatment options for patients with a reduced distal radius fracture, namely a directly after reduction applied splint or circumferential below-elbow cast, in a cluster randomized trial. All patients will be included at the emergency room of one of the participating hospitals. Randomization at patient level will be challenging because of the 24/7 availability of the emergency room in 10 participating hospitals and a high number of treating physicians. To overcome potential many protocol violations, randomization will take place on hospital level, with a cross-over point halfway the needed inclusions per hospital (i.e. after 30 inclusions). Meaning that all patients consulting to one hospital will receive the same intervention, which will change after half of the patients are included. The cross-over design will be used to overcome potential non-eligibility of both groups because the population that consult one hospital may differ from another hospital. Both interventions will be implemented by training the physicians of the participating hospitals by an experienced cast technician.
Patients will be followed for 12 months.

4. STUDY POPULATION

4.1 Population (base)

All consecutive patients visiting the emergency room with a displaced fracture of the distal radius, of one of the participating hospitals will be invited to participate.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria: 18 year or older, with a primary displaced fracture of the distal radius which is treated conservatively after closed reduction, and who are willing to comply with the study protocol.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study: failure to reach proper fracture alignment (5) after reduction(s) in the emergency room, inability to complete study forms due to any mental status or insufficient command of the Dutch language, both-bone forearm fracture (styloid ulnae fracture excluded), concomitant injuries to ipsilateral extremity or multi-traumata.

4.4 Sample size calculation

The needed numbers were calculated based on the results of our recent study (non-published data). The hypothesis is that at the end of the study the group of patients treated with a circular cast will have 10% re-displacements, whereas the group of patients that were treated with a splint will have 20% re-displacements. Randomization will be done at the hospital level, with a cross-over point at the middle of the inclusion period. To detect superiority of circular below-elbow cast compared to below-elbow splint, 550 patients are needed. The sample size calculation is based on a mixed effects logistic regression, to account for clustering using a random intercept for the hospitals. The intra-class correlation coefficient between the different hospitals for the proportion of secondary displacements is assumed to be 0.06, which is generally reported in literature for hospital processes. From the expected proportions of secondary displacements in the two groups we calculate the hospital specific log odds of secondary displacement in the cast group, equal to -2.275 and log odds ratio of secondary displacement between the two groups equal to 0.84. This calculation is based on the formula that links the cluster-specific coefficients in the mixed effects logistic regression with the population coefficients averaged over the hospitals. Based on this specification 200 datasets have been simulated under this setting and analyzed using a mixed effects logistic regression. For each simulated dataset a Wald test was used to test whether the marginal (averaged over the hospitals) log odds ratio between the groups was statistically different than 0 using a significance level of 5%. With a power of 93% 50 patients per hospital need to be included, resulting in a total number needed patients of 550 (11 participating hospitals). Additionally, we also calculated the needed number of patients by using two-sample test for proportions. Using the same assumptions, namely difference between groups, significance level of 0.05 and a power of 90%. This resulted in 530 needed patients in total. Accounting for a 10% loss to follow-up, a total of 610 patients (305 patients per group) are required.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

a) The fracture will be initially immobilized with circumferential below-elbow cast.
b) The fracture will be initially immobilized with below-elbow splint.

5.2 Use of co-intervention

NA

5.3 Escape medication

NA

6. INVESTIGATIONAL PRODUCT

NA

6.1 Name and description of investigational product(s)

6.2 Summary of findings from non-clinical studies

6.3 Summary of findings from clinical studies

6.4 Summary of known and potential risks and benefits

6.5 Description and justification of route of administration and dosage

6.6 Dosages, dosage modifications and method of administration

6.7 Preparation and labelling of Investigational Medicinal Product

6.8 Drug accountability

7. NON-INVESTIGATIONAL PRODUCT

NA

7.1 Name and description of non-investigational product(s)

7.2 Summary of findings from non-clinical studies

7.3 Summary of findings from clinical studies

7.4 Summary of known and potential risks and benefits

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Difference between groups in proportion of fracture re-displacement of the initial reduced distal radius fracture. Displacement of the radius is defined by the Dutch guideline (8); > 15^0 of dorsal angulation, > 20^0 of volar angulation, < 15^0 of inclination, > 5 millimeter shortening, and > 2 millimeter step-off or gap.

8.1.2 Secondary study parameters/endpoints (if applicable)

- pain medication use
- surgical interventions
- physical examination of range of motion of the arm and grip strength
- recovery of functioning: QUICK-DASH and PRWE questionnaires
- change in pain severity: number rating scale (NRS) for pain
- general quality of life: EQ-5D-5L
- total costs: intramural and extramural medical costs (iMCQ) and productivity loss (iPCQ)
- adverse events.

8.1.3 Other study parameters (if applicable)

Baseline characteristics will be recorded (age, gender, race/ethnicity, body mass index (BMI), educational status, marital status, living arrangements, employment status (full-time, part-time, unemployed) and musculoskeletal comorbidities, other comorbidity, duration of complaints, previous surgery.

8.2 Randomisation, blinding and treatment allocation

Randomization at patient level will be challenging because of the 24/7 availability of the emergency room in 10 participating hospitals and a high number of treating physicians. To overcome potential many protocol violations, randomization will take place on hospital level, with a cross-over point halfway the needed inclusions per hospital (i.e. after 27 inclusions). Meaning that all patients consulting to one hospital will receive the same intervention, which will change after half of the patients are included. The cross-over design will be used to overcome potential non-eligibility of

both groups because the population that consult one hospital may differ from another hospital.

8.3 Study procedures

Eligible patients seen at the emergency room will be informed about the study and invited to participate by the physician. Besides, the patient will receive written information. Because of the acute status of the complaints (distal radius fracture), direct start of treatment will be asked. If they are willing to participate, they will be screened for eligibility. The consequence of this procedure is that the baseline measurements will be carried out one day after the inclusion. Patients will be asked to fill in questionnaires (web-based system, Gemstracker). Randomization as reported before will take place at hospital level. When the patient conforms to the inclusion criteria and gives written informed consent, the study procedures can be started. Because of the need to include the patient before reduction of the fracture, the consequence will be that patients will be asked to sign the informed consent form before all exclusion criteria can be checked. The exclusion criterion "failure to reach proper fracture alignment after reduction(s) in the emergency room" can be checked on a radiograph after reduction and casting. After given informed consent all included patients will be followed. Only those patients that fulfill all- in and not the exclusion criteria will be seen as the CAST study population (see "stroomschema").

In table 1 an overview (appendix) of all measurements is given. At baseline we will collect baseline characteristics. At follow-up, recovery will be assessed by physically examining the range of motion of the arm and grip strength (hand dynamometer). Furthermore, patient experienced recovery of physical functioning will be assessed by the Quick-DASH (Disabilities of Arm, Shoulder and Hand) questionnaire, Patient-Rated Wrist Evaluation score (PRWE); and pain severity by number rating scale (NRS) for pain. All these outcomes are widely used and validated for patients with fractures of the wrist and arm.

Postero-anterior and lateral radiographs will be taken before and after reduction, and during follow- up at 1, 2 weeks, and at cast removal.

EQ-5D-5L use is recommended for the assessment of quality of life in trauma patients, especially for economic assessments. The patients' EQ-5D-5L health states will be converted into utility scores using the Dutch tariff. The EQ-5D-5L will be used for the cost-utility analysis.

Costs for health care and production loss will be measured using a questionnaire that is based on the Medical Consumption Questionnaire (iMCQ) and Production Consumption Questionnaire (iPCQ), validated by the Institute of Medical Technology Assessment (Erasmus University, Rotterdam, The Netherlands). iMCQ includes details on medical

specialist care, physical therapy, hospitalization, nursing home, home care, and other costs directly associated with diagnosis, treatment and rehabilitation. iPCQ includes details on work resumption and production losses.

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)

8.5 Replacement of individual subjects after withdrawal

No.

8.6 Follow-up of subjects withdrawn from treatment

Following usual care evaluations.

8.7 Premature termination of the study

NA

9. SAFETY REPORTING

9.1 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 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, SAEs and SUSARs

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 investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 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 hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- 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 judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

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.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

NA

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in:
   - Summary of Product Characteristics (SPC) for an authorised medicinal product;
   - Investigator's Brochure for an unauthorised medicinal product.

The sponsor will report expedited the following SUSARs through the web portal

ToetsingOnline to the METC *<reporting via webportalToetsingOnline is only applicable for investigator initiated studies>*:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.
The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

9.3 Annual safety report

NA

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 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

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

NA

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

The difference between groups in proportion of fracture re-displacement of the initial reduced distal radius fracture will be used as primary outcome. The hypothesis is that at the end of the study the group of patients treated with a circular cast will have 10% re-displacements, whereas the group of patients that were treated with a splint will have 20% re-displacements.
Patients will be analyzed according to the intention-to-treat principle.
The primary analyses will be performed by using a mixed effects logistic regression, to account for clustering using a random intercept for the hospitals. Fixed effects will be the covariates we adjust for as reported in the literature, namely age, presence of osteoporosis (yes/no), and fracture characteristics. If new prognostic factors will be identified and reported in literature, these factors will be added as covariate(s).

10.2 Secondary study parameter(s)

Difference between groups in recovery of function and grip strength, recovery of pain severity, and quality of life will be used as secondary outcomes. The analyses will be performed by using linear mixed models for repeated measures, with change in scores between baseline and the follow-up measurements at 1, 2 and 6 weeks and 3, 6 and 12 months as outcome.

COST EFFECTIVENESS ANALYSIS (CEA)

An economic evaluation will be conducted from a societal perspective in accordance with the Dutch guidelines (13) in which medical costs and loss of productivity costs will be considered. The time horizon will be 1 year to include all relevant costs and effects.
Both a cost-effective (CEA) and cost-utility (CUA) analysis will be performed. Direct intramural and extramural care costs will be calculated (e.g. radiographs, CT scan, casts, pain medication use, outpatients visits, surgical interventions, physiotherapy, hospital days, costs of side effects) and indirect non-medical costs (e.g. productivity losses). Data on medical resource use will be collected from the electronic hospital information systems, based on the iMTA Medical Consumption Questionnaire (iMCQ).
For the calculation of medical costs, we will use charges as published in Dutch guidelines as a proxy of real costs (13). The unit price of the cast and splint placement in patients with DRF will be calculated with the micro-costing method. Productivity costs will be registered in detail by the iPCQ.
The economic evaluation of a cast instead of a splint in reduced DRFs will be calculated as the incremental cost-effectiveness ratio (ICER). The primary effect outcome measures will be number of secondary replacements for the CEA and quality adjusted life years (QALY) for the CUA. QALYs will be measured for a 2 year period, based on the Dutch tariff for the EQ-5D-5L.
The sensitivity analysis will assess the robustness of the results to changes in costs and effect parameters. Bootstrapping with 5000 replications will be used to estimate 95% confidence intervals around cost differences and the uncertainty surrounding the ICERs. This will be graphically presented on cost-effectiveness planes and acceptability curves using the net benefit framework (14). Cost-effectiveness acceptability curves show the probability that the intervention is cost-effective in comparison with usual care for a range of different ceiling ratios thereby showing decision uncertainty. For the time horizon of 24 months, discounting is not necessary.

BUDGET IMPACT ANALYSIS (BIA)

The BIA will be performed following principles for good practice (15). Results of the economic evaluation will be linearly extrapolated over a period of 5 years to estimate the financial consequences of wide-spread implementation of a cast instead of a splint in reduced DRFs in the Dutch healthcare system. Furthermore, national incidence data will be used. Analyses will be performed for the societal-, Budgettair Kader Zorg (BKZ)-, health insurer's- and health care perspective. Within the BKZ perspective we will estimate the effect on the medication budget and specialized medical care budget. The intervention's effectiveness of this study will be extrapolated by a Markov model. Different scenario's will be considered in the BIA; a) usual care, b) scenario with gradual implementation (e.g. 80%) over time. The proportion and

characteristics of the target population will be estimated using Dutch epidemiological data. For each perspective different prices will be used. In the societal and health care perspective standard prices will be used (13). For the BKZ and health insurer's perspective tariffs established by the Dutch Healthcare Authority (Nederlandse Zorgautoriteit) are used. Sensitivity analysis will be done on parameter uncertain parameters (e.g. % implementation, and optimization of the ACL treatment algorithm) and structural uncertainty (assumptions in the framing of the BIA).

10.3 Other study parameters

NA

10.4 Interim analysis (if applicable)

NA

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (64th version, date, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts .

11.2 Recruitment and consent

Eligible patients seen at the emergency room, because of a trauma which resulted in a distal radius fracture and fit to the inclusion and exclusion criteria, will be informed about the study and invited to participate by the physician. Besides the patient will receive written information. Because the treatment has to be started directly during the visit of the patient, the patient has only a short period of time (half of an hour) to decide whether he/she is willing to participate.

If the patient is interested the physician will check whether the patient fits to the inclusion and not to the exclusion criteria. If the patient fits and sign the informed consent form they will receive the baseline questionnaire by email. The consequence of this is that the baseline measurements will be collected one day after inclusion and start of the intervention.

11.3 Objection by minors or incapacitated subjects (if applicable)

NA

11.4 Benefits and risks assessment, group relatedness

NA

11.5 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.

11.6 Incentives (if applicable)

NA

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Personal data of the participating patients that will be collected during the study, will be changed by a study number. This number will be used for all study documentation, and all study reports or publications. The key of this study number will be handled by an independent researcher. All data will be stored during the study period, and if the patient give informed consent for a total of 15 years.

12.2 Monitoring and Quality Assurance

The study will monitored according to the monitoring plan (document K).

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable 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 Temporary halt and (prematurely) end of study report

The investigator/sponsor 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.

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.

12.6 Public disclosure and publication policy

NA

13. STRUCTURED RISK ANALYSIS

NA

13.1 Potential issues of concern

NA

a. Level of knowledge about mechanism of action

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

d. Selectivity of the mechanism to target tissue in animals and/or human beings

e. Analysis of potential effect

f. Pharmacokinetic considerations

g. Study population

h. Interaction with other products

i. Predictability of effect

j. Can effects be managed?

13.2 Synthesis

NA

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