TEMPLATE RESEARCH PROTOCOL

(September 2018)

- - May 2015: adaptation section 11.5: text in accordance to old and new Measure regarding Compulsory Insurance for Clinical Research in Humans
- - Sept 2015: adaptation section 9.1, 9.2 and 12.5: text in accordance to WMO amendment on reporting SAE and temporary halt (section 10 of WMO)
- - Oct 2015: adaptation section 4.4 – comment [CCMO15], 8.2 and 10.1 with respect to methodology/statistics
- - Sept 2018: adaptation section 12.1 and comment [CCMO46] due to applicability GDPR as of May, 2018

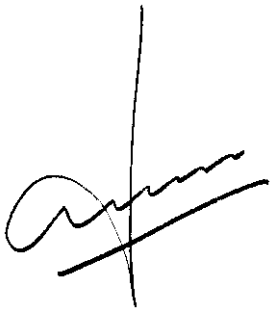
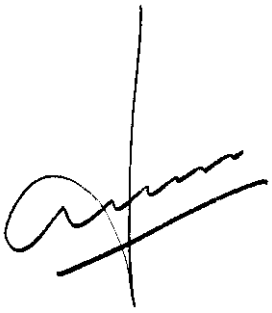
PROTOCOL

Conservative or surgical treatment for mild cervical spondylotic myelopathy: a multi-center randomized controlled trial

Protocol ID	2021-13139
Short title	treatment mild CSM
Acronyme	COSU trial
EudraCT number	n/a
ISRCTN number	
Version	2
Date	November 12, 2021
Coordinating investigator/project leade	Ronald HMA Bartels, MD, PhD Professor and Chairman Department of Neurosurgery Radboud University Medical Center Geert Grooteplein-Zuid 10 6525 GA Nijmegen the Netherlands Phone: + 31 24 3615200 www.nccn.nl
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder) ***<Multicenter research: per site>***	- Radboudumc, Ronald Bartels, Ronald.bartels@radboudumc.nl - CWZ, Martine van Bilsen, martine.vanbilsen@radboudumc.nl - LUMC, Carmen Vleggeert-Lankamp, c.l.a.vleggeert-lankamp@lumc.nl

	- Rijnstate Ziekenhuis, Job van Susante, jvansusante@rijnstate.nl - Haaglanden Medische Centrum, Mark Arts, m.artshaaglandenmc.nl - Sint Martenskliniek, Maarten Spruit, m.spruit@maartenskliniek.nl
Sponsor (in Dutch: verrichter/opdrachtgever)	Radboudumc Department of Neurosurgery
Subsidising party	Application ZonMW grant, awaiting for decision
Independent expert (s)	Wim Mulleners Canisius Wilherlmina Ziekenhuis w.mulleners@cwz.nl
Laboratory sites <*if applicable*>	n/a
Pharmacy <*if applicable*>	n/a

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or legal representative: Jan Smit, MD, PhD, dean and board member Radboud University Medical Center Geert Grooteplein-Zuid 10 6525 GA Nijmegen the Netherlands **Head of Department:** Ronald HMA Bartels, MD, PhD Professor and Chairman Department of Neurosurgery Geert Grooteplein-Zuid 10 6525 GA Nijmegen the Netherlands Phone: + 31 24 3615200 www.nccn.nl		October 25, 2021
Project leader: Ronald HMA Bartels, MD, PhD Professor and Chairman Department of Neurosurgery Radboud University Medical Center Geert Grooteplein-Zuid 10 6525 GA Nijmegen the Netherlands Phone: + 31 24 3615200 www.nccn.nl		October 25, 2021

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (AB form), the application form that is required fo submission to the accredited Ethics Committe**

	in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Hum 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, f 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, l referred to as a subsidising party.
SUSAR	**Suspected Unexpected Serious Adverse Reacti**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects A in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Cervical spondylotic myelopathy (CSM) is a common cause of spinal disfunction affecting dexterity, walking ability and self-independence. Due to an ageing population its incidence will increase. For the more severe grades of CSM surgical decompression is generally accepted as treatment of choice. The objective of surgery is to maintain the current clinical situation with slight possibility of improvement. For a mild CSM, however, it is not clear which treatment is the best, conservative or surgical treatment. Although some reports show benefit for decompressive surgery, it is still not proven which treatment has the best clinical result.

Objective: The primary objective is the investigate whether surgical decompression is more beneficial than conservative treatment in case of mild CSM. The second objective is to evaluate if surgery is more cost-effective than conservative treatment.

Study design: The study is designed as a multi-center randomized controlled trial with an economic evaluation alongside. Due to the character of the interventions, blinding of patients nor researchers is not possible.

Study population: Table 1: Inclusion and exclusion criteria

Inclusion	**Exclusion**
Adult patients	Non-fluent in Dutch language
Signs and symptoms of cervical myelopathy	Soft disc as causative pathologic mechanism
Radiologic signs of degenerative compressive cervical myelopathy	Coexisting diseases that cause signs and symptoms interfering with those of CSM, e.g., plexopathy, cerebrovascular incident, polyneuropathy due to diabetes mellitus, etc.
mJOA ≥ 15	Alcohol abuse (more than two units daily)
	mJOA < 15

	Previous history of neck surgery
	Non-degenerative CSM

Intervention: Surgical decompression of the cervical spinal cord will be compared with supervised conservative treatment. Both treatments are standard care in the Netherlands.

Main study parameters/endpoints: The primary outcome is the difference in an adaptation of the 10-s grip and release (G&R) test that resulted in a quantitative assessment of the function of the hand movement during a 15-s video. The secondary outcome measurements are: mJOA, neck disability index (NDI), EQ-5D-5L, NRS neck pain, complications, healthcare resource use, and work productivity.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Since both treatments are usual and accepted in current clinical practice, participation does not generate an extra burden or will expose patients to extra risks.

1. INTRODUCTION AND RATIONALE

Although CSM is reported to be the most common cause of spinal cord disfunction(6), its prevalence is not clear. The incidence of hospitalization due to CSM-related disorders in the U.S. is estimated at 4.04 per 100,000 person-years(7). In the Netherlands, admissions for the surgical treatment of CSM were estimated to be 1.6 per 100,000 inhabitants(8). Men are more frequently affected than women, and the average age of diagnosis is around 65 years(9).

CSM is caused by progressive degenerative processes within the spine. Compressive, shearing, and tethering forces, in combination with inflammatory responses, contribute to the dysfunction of the spinal cord(10). The speed at which the degenerative process progresses is variable; the natural course of CSM varies from a gradual decline to a sudden and major deterioration. The clinical presentation can differ in severity from mild to severe and is dependent upon the degree of neurologic deficit in the arms and/or legs. Patients with mild symptoms are generally younger than those with moderate or severe CSM(1).

A system for scoring the degree of neurologic deficit was developed by the Japanese Orthopedic Association (JOA)(11), and was later modified (mJOA) for western populations(12) who do not commonly eat using chopsticks. The mJOA has been translated into the Dutch language(13). Typically, patients with a mild CSM have a mJOA score of 15 to 17, whereas those with a mJOA score between 12 and 14 are considered to have moderate disease. Severe CSM is defined as a mJOA score of 0–11 (14). Patients presenting with mild CSM are typically much younger than the total group of patients with all grades of severities of CSM. In a study by Bond et al.(15), the mean age was 54.8 ± 12.6 years, indicating they are generally still in the working phase of life.

For patients presenting with moderate and severe CSM, a surgical decompression of the spinal cord is recommended(16). The major goal is the stabilization of the clinical situation with a possibility for improvement(17). A study by Bahiwala et al. showed that nearly half of these patients did improve, whereas the remaining patients showed small improvements that did not reach the minimal clinically important difference (MCID)(17). Despite adequate surgery, a minority of patients might further deteriorate, indicating that the spinal cord disease is progressive. Furthermore, the severity of the clinical situation, age of the patient, and duration of the complaints can predict the outcome(1, 18, 19).

The proper treatment of patients with mild CSM is still under debate. Despite several comparative studies investigating conservative versus surgical interventions, a clear advantage for decompressive

surgery has not been demonstrated(20). Several studies do favor decompressive surgery(21); however, with the exception of small retrospective studies, the lack of a uniform definition of conservative treatment adds uncertainty to this finding. Another very important factor is the use of mJOA as an outcome scale; although an improvement after treatment may be very relevant for the patient, it might not be expressed by a change in mJOA. Even if a change is detected, it might not reach MCID, and since mild CSM is defined as a mJOA score > 14, a ceiling effect is also present. These findings have been confirmed by recent systematic reviews(20, 22, 23).

In 2017, a multidisciplinary guideline group recommended surgical intervention or supervised conservative treatment for patients presenting with mild CSM(16). This recommendation is still in place today(15, 24); however, considering the natural course of CSM and the predictive factors, it seems logical to intervene surgically in the early stages of the disease. A soft disc causing mild CSM might be an exception, since these may fully recover after conservative management(25). Recently, it was shown in an observational non-comparative study that significant gains in functional status, level of disability, and quality of life are obtained after surgical intervention for mild CSM(24).

2. OBJECTIVES

The primary objective is the investigate whether surgical decompression is more beneficial than conservative treatment in case of mild CSM. The second objective is to evaluate if surgery is more cost-effective than conservative treatment.

3. STUDY DESIGN

The study is designed as a multi-center randomized controlled trial with an additional economic evaluation. Due to the character of the interventions, the blinding of patients and researchers is not possible.

Study timeline

	Baseline	**Start treatment Surgery/ conservative treatment**	**Six weeks after treatment**	**Three months after treatment**	**One year after treatment**	**Two years after treatment**
Physical exam	X					
15-s G&R test	X		X	X	X	X
mJOA	X			X	X	X
EQ-5D-5L	X			X	X	X
Complications		X	X	X	X	X
iMCQ	X			X	X	X
iPCQ	X			X	X	X

4. STUDY POPULATION

4.1 Population

Adult patients suffering from the symptoms and signs of mild CSM with a mJOA score of 15 to 17 are eligible for the study and will be included after they have given written informed consent. The radiological imaging of these patients should include at least an MRI or CT scan. Standard cervical X-rays and dynamic X-rays are recommended. A side of compression explaining the clinical condition should be shown at these radiological investigations.

Definition of mild CSM

Patients with suspected mild CSM present with symptoms and signs suggesting an involvement of the spinal cord. They often have bilateral complaints: tingling in both hands, numbness in both hands, and a discrete loss of motor function in both hands/arms. They complain often of difficulty walking, such as staggering, loss of coordination, or stumbling. Micturition might be slightly disturbed, with some patients reporting stress incontinence and occasionally urge incontinence. Upon neurologic examination, a sensory and/or motor deficit might be found. Reflexes might be increased, but abnormal reflexes are not obligatory. The mJOA score is ≥ 15.

These findings should be explained by the radiological imaging. The spinal canal is narrowed due to degenerative changes in patients with CSM. If a soft disc is the cause of the patient's symptoms, they are excluded from the study because it is likely that they recover with conservative treatment.

4.2 Inclusion criteria

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

Inclusion
Adult patients
Signs and symptoms of cervical myelopathy
Radiologic signs of degenerative compressive cervical myelopathy

mJOA ≥ 15

4.3 Exclusion criteria

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

Exclusion
Non-fluent in Dutch language
Soft disc as causative pathologic mechanism
Coexisting diseases that cause signs and symptoms interfering with those of CSM, e.g., plexopathy, cerebrovascular incident, polyneuropathy due to diabetes mellitus, etc.
Alcohol abuse (more than two units daily)
mJOA < 15
Previous history of neck surgery
Non-degenerative CSM

4.4 Sample size calculation

The 15-s G&R test is a quantitative assessment tool. An MCID has not been estimated. In the original description of this tool(28), the numbers of cycles in normal and CSM patients were 32.5 ± 9.0 and 22.9 ± 8.7, respectively; however, the mean mJOA score of the patient group was 10.2 ± 2.7, indicating that the patients suffered from moderate or severe CSM. The patient postoperative score was 34.9 ± 7.6, representing a significant clinical improvement that was confirmed by the postoperative mJOA score of 14.2 ± 2.1. From this point of view, an MCID of 12 cycles could be assumed, but for patients with mild CSM, the improvement in cycles is expected to be lower since they might start with a higher baseline value. We estimated the MCID for the mild CSM at 6 ± 7.

The sample size is calculated assuming a superiority design with an intention-to-treat analysis. A superiority design was chosen, since it is hypothesized that surgical decompression has a better outcome. A difference at 24 months after the start of treatment between the conservative and the surgical group of 6 in the 15s G&R test is considered clinically relevant.

Assuming a two-sided approach with $\alpha = 0.05$ and a power of 90%, the sample size is set to 30 patients per group. Ten percent of patients are predicted to drop out before the follow up is complete; thus, the sample size is increased to 33 patients per group. Crossover from the conservative to the surgical group is also expected, since degeneration might progress and symptoms become worse during the study period; therefore, the final sample size is set at 40 per group.

5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

Surgery

The goal of surgical intervention is the decompression of the spinal cord to halt the progression of the disease and facilitate recovery. Several approaches are possible: laminectomy with or without fusion, laminoplasty with or without fusion, anterior discectomy with fusion, corpectomy, or a circumferential approach. None of them has been proven superior. The choice of approach is dependent upon the levels of compression, the shape of the cervical spine, instability of the cervical spine, and also the preference of the surgeon; therefore, the surgical approach is at the discretion of the treating surgeon.

Conservative treatment

Supervised conservative therapy will also be used. The patients are referred to a physical therapist to practice hand function and improve their walking abilities. During the study, the patients are contacted via video calls to evaluate their clinical condition. If the symptoms and signs worsen, the patients are invited to the outpatient clinic. A physical examination is performed, and surgical decompression may be offered as treatment if the neurologic condition worsens or if the patient's conviction is altered during the course of the treatment. The reason for offering surgical decompression will be noted.

METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Since only patients with mild signs and symptoms will be included, difference in outcome will not be shown by mJOA due to its ceiling effect. Therefore, mJOA is not appropriate as primary outcome measurement for evaluating the effect of treatment in mild CSM. Furthermore, since loss of dexterity, even minimally, can seriously affect the quality of life, the primary outcome will focus on function of the hand. It is also known that digital clumsiness precedes any other weakness in CSM patients. Therefore, the 10s grip and release test seems to be an adequate outcome measurement(24). However, the adaptation by Hosono et al. makes evaluation at any time and any place possible. The method is valid and reliable(25). It is an quantitative assessment of the function of the hand. During 15 s video hand movements are registered, for which purpose currently cellular phones can be used. Since the patients are allocated at random, differences that might occur to age and gender(26) are not taken into consideration. The result per test will be represented by worst score comparing of the left and the right hand.

8.1.2 Secondary study parameters/endpoints (if applicable)

As secondary outcome measurements are chosen: mJOA, neck disability index (NDI), SF36, and complications. The mJOA is a well-accepted outcome measure for patients with a CSM. It addresses three domains: function of the hand, walking ability and micturition. It is a numeric scale with score ranging from 0 to 17 points. 17 Points indicate absence of signs or symptoms. Mild CSM is defined as mJOA ranging from 15 to 17. The translation in Dutch has been validated(13). It is not expected that a minimal clinically relevant difference will be expressed by a change in mJOA. The MCID is 1 for mild CSM(27). The NDI is a widely use outcome measure. It is a reliable and validated self-reported outcome measure for patients with neck pain(28). A Dutch validated version is available(29). It measures neckpain, and restriction in activities related to work as well as those without a relation to work. The numeric scale ranges from 0-50, and zero means no complaints or restrictions. MCID for NDI was set at 7.5 for evaluating treatment of cervical degenerative disc disease The EQ-5D-5L is a generic questionnaire developed by the EuroQol group in 2005 to assess the quality of health-related quality of life. Compared to the previous version (EQ-5D-3L) EQ-5D-5L has fewer ceiling effects. It is also

significantly more sensitive, so, small changes in mild situations could be detected(31). A Dutch version is available and the preferences for the Dutch population are known(32).
Complications will be registered. A complication is any unforeseen and unwanted outcome after installment of a treatment. To address a complication as surgery related, it should occur with 31 days after surgery. Unscheduled cervical re-surgery during the study period is considered as a complication. In some cases, a surgical plan may include two stages which should not necessarily be on the same day. Since this is scheduled, it will not be registered as a complication.
cost-effectiveness
Two questionnaires developed by Institute for Medical Technology Assessment from the Erasmus University Rotterdam, the Netherlands (IMTA) are used for evaluation off health economics, the iMTA Productivity Cost Questionnaire (iPCQ)(33) and the iMTA Medical Consumption Questionnaire (iMCQ)(34). iPCQ is a short generic measurement instrument to evaluate the impact of disease on the ability of a person to perform work. Costs can be calculated by scoring- and valuation methods. iMCQ is a generic instrument for measuring medical costs, and includes questions related to frequently occurring contacts with health care. In addition to this questionnaires information about hospital related costs (e.g. length of stay and costs related to surgery) will be collected through hospital databases. iPCQ can be used in combination with iMCQ. iPCQ and iMCQ are translated into Dutch.

8.1.3 Other study parameters (if applicable)

Other parameters are not included.

8.2 Randomisation, blinding and treatment allocation

For the treatment group allocation, a variable block randomization method is chosen. For this purpose, an online data system, CastorEDC (EU HQ, Amsterdam, the Netherlands), is used. Variable block sizes of four, six, and eight will be used and stratified by treatment center. Patients will be randomized in a 1:1 ratio to conservative treatment or surgical decompression. The randomisation sequence was generated by an independent statistician Each patient will be given a unique study number. The web-based system will be supervised by the Clinical Trial Center of Radboud university medical center. Randomization will take place after the patients provide informed consent to participate. A designated member of the site team, usually a clinician or nurse involved in the participant's care, did the online randomization.

8.3 Study procedures

All patients are seen by orthopedic surgeon or neurosurgeon dedicated to cervical spinal surgery. If the diagnosis of mild CSM is confirmed the trial will be mentioned as will be the possibility to participate. After five days the patients will be contacted, and after given informed consent they will be randomly allocated to the surgical or conservative treatment group. At baseline, a physical examination has been performed and mJOA has been completed. After approval to participate, the other outcome measurements can be completed online. For the 15s grip and release test an investigator will have contact with the patient by video calling. Patients are scheduled for surgical decompression or referred to the physical therapist for training of hand function and walking. The date of the surgery or the first conservative treatment is considered as the date of the treatment. All outcome measurements can be obtained through a web-based method except for the 15s video grip-and-release test, which can be done by video calling. If patients are not convenient with web-based methods of video calling, aa appointment at the outpatient clinic is always possible. The trial should not interfere with the usual practice for the patients in the participating hospitals. In the following time line the follow-up moments with outcome measurements are shown.

	Baseline	**Start treatment Surgery/ conservative treatment**	**Six weeks after treatment**	**Three months after treatment**	**One year after treatment**	**Two years after treatment**
Physical exam	X					
15-s G&R test	X		X	X	X	X
mJOA	X			X	X	X
NDI	X			X	X	X
EQ-5D-5L	X			X	X	X
Complications		X	X	X	X	X

iMCQ	X			X	X	X
iPCQ	X			X	X	X

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)

Patients allocated to the conservative treatment with aggravation of signs and symptoms due to CSM might be offered surgical treatment. They will not be withdrawn from the trial but considered as cross overs.

8.5 Replacement of individual subjects after withdrawal

Loss to follow up is included in the sample size calculation

8.6 Follow-up of subjects withdrawn from treatment

We will try to contact them after the last patient has completed all follow up outcome measurements. However, we are aware that the patients who left the study for any reason might be reluctant to cooperate.

8.7 Premature termination of the study

Since the treatment that are compared are standard care for mild CSM and participating surgeons are dedicated to cervical spinal surgery, it is not expected that a major event will occur necessitating premature termination of the study. However, if in the conservative treatment group more than 50% of the patients will cross over to surgical treatment after inclusion of 40 patients after at least one year follow-up one might reconsider this.

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 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.

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 trial procedure. 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; 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.

Alle SAEs will immediately been reported to the project leader, who will report all SAEs to the sponsor and the DSMB without undue delay after obtaining knowledge of the events. SAEs related to this trial are death, hemorrhage with compression of the spinal cord resulting in additional neurologic deficit, and hemorrhage with compression of the airway (anterior approach). During conservative treatment worsening of the clinical situation is not considered as a SAE, but as a possibility due to the progressive nature of the disease.

The project leader 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 DMSB has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

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]

A DSMB is installed. The members are prof. dr Y. Temel who will act as chair, dr W. Verhagen, neurologist ret, and dr D. Verbaan, epidemiologist/statistician. The role of the DSMB is to protect and serve trial patients (especially re: safety) and to assist and advise the project leader to protect the validity and credibility of the trial. The tasks of the DSMB are described in the DSM and can be summarized as interim review of the trial's progress including updated figures on recruitment, data quality, and main outcomes and safety data. A clear reason for stopping the trial is when more than 50 % of the patients crossover from conservative group to surgical group

The advice(s) of the DSMB will only be sent to the sponsor/project leader of the study. Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

10. STATISTICAL ANALYSIS

Continuous variables will be represented as means ± standard deviation (SD). If the distribution is non-normal, the data will be presented as medians with interquartile ranges (IQR). Normality will be graphically checked.

The primary outcome is a difference in the 15-s G&R test at two years after randomization. For this analysis, generalized linear mixed models (GLMMs) will be used to account for repeated measurements of patients and multicenter stratification.

Secondary outcomes, mJOA, NDI and EQ-5D-5L will also be analyzed using a GLMM. The estimation of the main effect at 24 months, adjusted for stratification factors, will be included in all analyses for the primary assessment of the treatment.

At 6 weeks, 3 months, 12 months and 24 months, the GLMM repeated measurement will be applied. The independent variables are group (conservative and surgery), time (follow-up timepoints), and the interaction between group and time (g × t). Dependent variables are the primary and secondary outcome parameters. Descriptive statistics are used to assess the complications. Using chi^2 or Fisher exact tests, the complications between groups will be compared.

The analysis will be performed according to the intention-to-treat principle. Due to the progressive nature of CSM worsening of the neurologic deficit of patients within the conservative arm might be expected, and surgical decompression of the spinal cord may be offered as a treatment. Therefore, an additional as treated analysis will be performed.

10.1 Primary study parameter(s)

The primary analysis will evaluate the difference between the surgical and conservative group in 15 s G&R test at 24 months after the start of the treatment. Since outcome will evaluate over time, we are also interested in outcome during the various follow up moments. Therefore, mixed models will be used to evaluate the outcome. Since outcome might be dependent upon time and treatment, an interaction between these will also be evaluated.

10.2 Secondary study parameter(s)

The secondary outcome measurements are mJOA, neck disability index (NDI), EQ-5D-5L, NRS neck pain, complications. Our sample size calculation has not taken these into account. Therefore, the analysis will have mainly a descriptive nature. The secondary outcome measurements, except for the complications will be evaluated at the various follow-up moments using mixed models. Although complications after surgery are defined as unexpected events within 30 days after surgery, we will not restrict the period to 30 days after start of treatment. Complications during the cornservative treatment can occur at any moment. Therefore, the difference between the two treatment groups in complications will be evaluated at 24 months using a chi square test.

10.3 Other study parameters

The cost-effectiveness analysis will be performed from a societal perspective, over a time horizon of two years, and will adhere to the Dutch guideline for economic evaluation(37). Resource use will be measured using the iMCQ questionnaire. Productivity loss will be measured using the iPCQ questionnaire. The unit costs will be based on the Dutch guideline for costing research. The unit of effect is the quality-adjusted life year (QALY). QALYs will be derived from the EQ-5D-5L, using the area under the curve method. Incremental Cost-Effectiveness Ratios (ICERs) will be calculated by dividing the difference in costs by the difference in QALYs. Uncertainty will be addressed by means of bootstrapping. Where relevant, sensitivity analyses will be performed to explore the impact of uncertain parameters on the ICER.

A budget impact analysis (BIA) will be performed in accordance with the ISPOR Principles of Good Practice for Budget Impact Analysis, using the ZonMw BIA tool.

10.4 Interim analysis (if applicable)

An interim analysis will not be performed

ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (9th July, 2018)) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

11.2 Recruitment and consent

The diagnosis of mild CSM is made by a neurologist. The referring neurologists are informed about the current trial. They will refer the patients to an orthopedic surgeon or a neurosurgeon familiar with cervical spine surgery. During the first visit at the outpatient clinic, the patient is informed about the trial and its purpose by the orthopedic surgeon or neurosurgeon. The patient information is offered to the patient. Patients are given five days to decide whether they are willing to participate to the trial. After the patient has given verbal informed consent, the patient is allocated to either the surgical arm or the conservative treatment arm. The research nurses will then provide the informed consent forms. After the first visit, contact with patients through the ehealth application (video calling) is preferred; however, local customs may prevail.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

11.4 Benefits and risks assessment, group relatedness

The proper treatment of patients with mild CSM is still under debate. Considering the natural course of CSM and the predictive factors, it is arguable to intervene surgically in the early stages of the disease. The major benefit of this trial is providing clarity about the best treatment for patients with mild CSM reducing practice variation of the treatment for this entity. Since both treatment options are standard care at this moment, participation to the trial will not create extra risks. Complications related to conservative treatment and surgical treatment are well known. Since the complications for surgery are related to the chosen approach (posterior, anterior, combination of both and many variations of each approach), they will not specifically be mentioned. The most important complication of any surgical treatment for this entity is aggravation of the neurologic deficit that rarely results in a complete spinal

cord lesion. Another well-known complication is a C5 palsy, that in most instances will resolve within 6 months.

11.5 Compensation for injury

The sponsor 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. Despite having the insurance, the METC Nederland Oost was asked for clearance of having this insurance since the risk attributed to participation to this trial is considered zero.

11.6 Incentives

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Data will be entered and stored into a web-based database (Castor-EDC), by local research personnel of each including center. Each patient will be identified with a unique study number. The local investigators will keep a list showing codes and names. Unique documents with identifying information will be stored separately from the study database in digital files, categorized by study number on a secure drive system. Hard copies containing identifying information will be stored in a locked closet at the participating centers. All documents containing identifying information will be only accessible to the local researcher and the quality monitor appointed by the principal investigator. All data will be stored for 15 years after completion of the study. Data will be handled according to the Dutch Personal Data Protection Act, Good Clinical Practice and other relevant regulations.

12.2 Monitoring and Quality Assurance

Monitoring the conduct of the study will done by evaluating the data by the DSMB as described in the Charter.

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.
Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor. (*Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation*.)

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 investigator/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

Please mention the arrangements made between the sponsor and the investigator concerning the public disclosure and publication of the research data. >

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