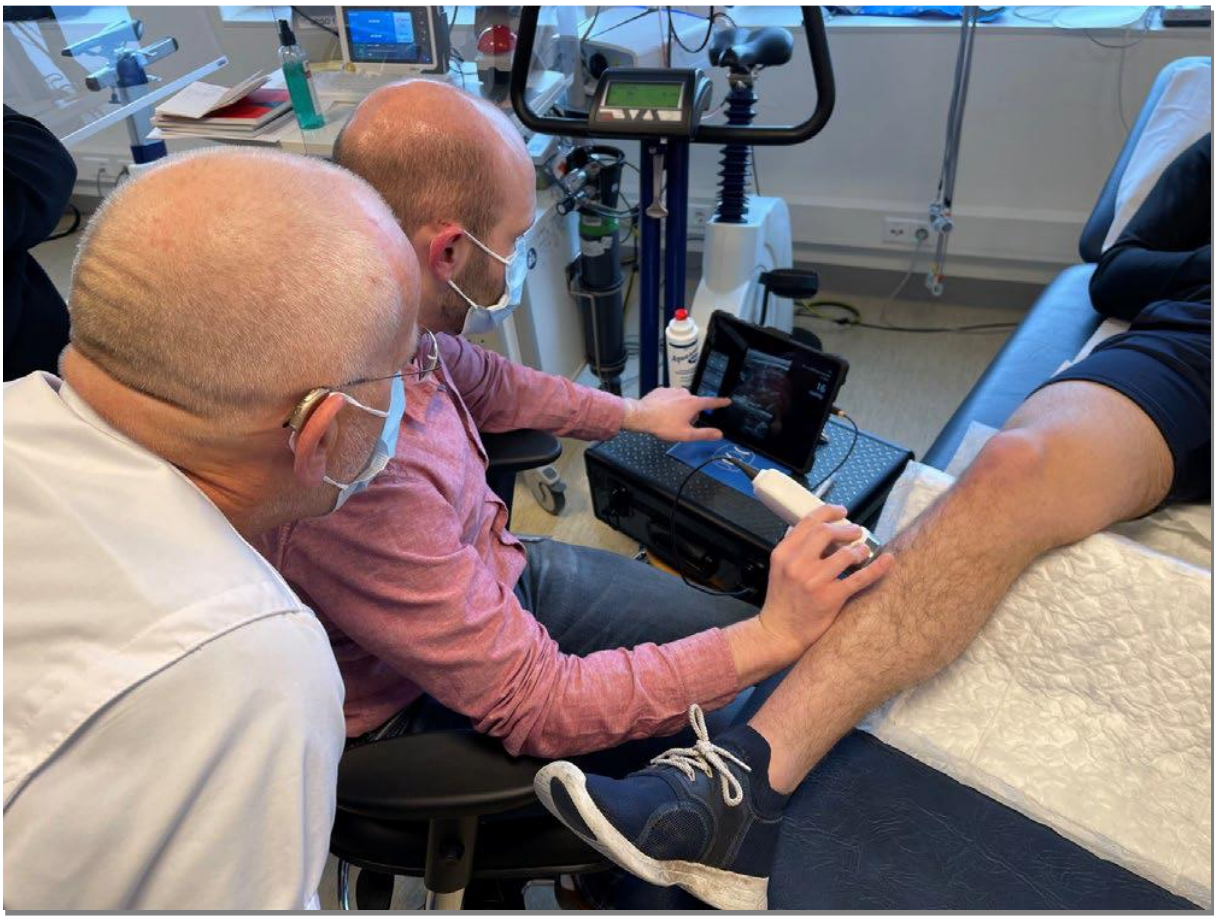
Validation of CPM#1 compressibility in healthy volunteers in rest and after exercise

(Version 2.2: 23/11/2022)



máxima mc

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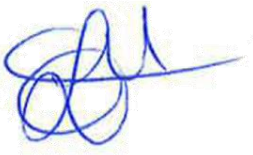
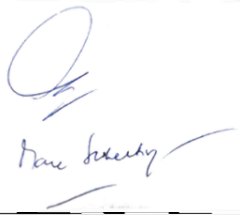
Head of Department: L. Van Leeuwen Manager Zorggroep Snijdend Máxima MC, Veldhoven		15-9-22
Principal Investigator: Dr. M.R.M. Scheltinga Surgeon Máxima MC, Veldhoven		16-9-'22

TABLE OF CONTENTS

1. INTRODUCTION AND RATIONALE 10
2. OBJECTIVES 11
3. STUDY DESIGN 12
4. STUDY POPULATION 12
4.1 Population (base) 12
4.2 Inclusion criteria 12
4.3 Exclusion criteria 12
4.1 Sample size calculation ..... **Fout! Bladwijzer niet gedefinieerd.**
5. TREATMENT OF SUBJECTS 13
5.1 Investigational product/treatment 14
5.2 Use of co-intervention (if applicable) 14
5.3 Escape medication (if applicable) 14
6. INVESTIGATIONAL PRODUCT 15
6.1 Name and description of investigational product(s) 15
6.2 Summary of findings from non-clinical studies 15
6.3 Summary of findings from clinical studies 15
6.4 Summary of known and potential risks and benefits 15
6.5 Description and justification of route of administration and dosage 15
6.6 Dosages, dosage modifications and method of administration 15
6.7 Preparation and labelling of Investigational Medicinal Product 15
6.8 Drug accountability 15
7. NON-INVESTIGATIONAL PRODUCT 15
8. METHODS 16
8.1 Study parameters/endpoints 16
8.1.1 Main study parameter/endpoint 16
8.1.2 Secondary study parameters/endpoints (if applicable) 16
8.1.3 Other study parameters (if applicable) 16
8.2 Randomisation, blinding and treatment allocation 16
8.3 Study procedures 17
8.4 Withdrawal of individual subjects 18
8.4.1 Specific criteria for withdrawal (if applicable) 18
8.5 Replacement of individual subjects after withdrawal 18
8.6 Follow-up of subjects withdrawn from treatment 18
8.7 Premature termination of the study 18
9. SAFETY REPORTING 19
9.1 Temporary halt for reasons of subject safety 19
9.2 AEs, SAEs and SUSARs 19
9.2.1 Adverse events (AEs) 19
9.2.2 Serious adverse events (SAEs) 19
9.2.3 Suspected unexpected serious adverse reactions (SUSARs) 20
9.3 Annual safety report 20

9.4 Follow-up of adverse events....20
9.5 Data Safety Monitoring Board (DSMB) / Safety Committee....20
10. STATISTICAL ANALYSIS....21
10.1 Primary study parameter(s)....21
10.2 Secondary study parameter(s)....21
10.3 Other study parameters....21
10.4 Interim analysis (if applicable)....21
11. ETHICAL CONSIDERATIONS....22
11.1 Regulation statement....22
11.2 Recruitment and consent....22
11.3 Objection by minors or incapacitated subjects (if applicable)....22
11.4 Benefits and risks assessment, group relatedness....22
11.5 Compensation for injury....22
11.6 Incentives (if applicable)....22
12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION....23
12.1 Handling and storage of data and documents....23
12.2 Monitoring and Quality Assurance....23
12.3 Amendments....23
12.4 Annual progress report....23
12.5 Temporary halt and (prematurely) end of study report....24
12.6 Public disclosure and publication policy....24
13. STRUCTURED RISK ANALYSIS....25
13.1 Potential issues of concern....25
13.2 Synthesis....26
14. REFERENCES....26

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**
CECS	**Chronic Exertional Compartment Syndrome**
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**
ICC	**Intraclass Correlation Coefficient**
ICPM	**Intra-Compartmental Pressure Measurement**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
NIAPS	**Netwerk Inspannings Afhankelijke PijnSyndromen; Dutch Network of hospitals that treat patients with CECS and developed a CECS-specific questionnaire including symptoms and function**
(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:

Chronic Exertional Compartment Syndrome (CECS) is one of the exercise-induced lower leg pathologies. Recognition by patients and physicians is not optimal. As a consequence, many patients are undiagnosed and are forced to stop their sporting activities. To diagnose CECS, a doctor should be alerted by a patient's history and a physical examination. If both suggestive of CECS, an invasive intra compartmental pressure measurement (ICPM) in the affected compartment may be performed. During the ICPM a catheter is placed into the muscle via a hollow needle. The ICPM is not flawless in terms of accuracy and reproducibility and has a low intra-observer reproducibility. Moreover, haematoma or other tissue damage may occur following an ICPM. Nevertheless, this *invasive* ICPM is in 2022 still considered the 'gold-standard' diagnostic tool for CECS, in the absence of a better one.

A novel non-invasive tool for CECS is possibly provided by measuring muscle tissue compressibility. The idea is, that muscle tissue with a high pressure (as in CECS patients) requires more external force to compress, compared to tissue with a low pressure. The study device used in this study, the CPM#1 device, is based on this principle. The CPM#1 device is non-invasive, not painful, very user friendly, and the measurement can be executed as an 'office procedure' in a couple of minutes. This study will focus on determining the reliability of the device in healthy volunteers.

Objective:

The primary objective is

- To validate the *inter*-observer reliability of compressibility measurements with the CPM#1 device during rest in healthy volunteers.

Secondary objectives are

- To validate the *intra*-observer reliability of compressibility measurements with the CPM#1 device during rest in healthy volunteers.
- To investigate the effect of exercise on compressibility immediately, one minute, and five minutes after exercise in healthy volunteers.
- To map the invasiveness of the compressibility measurement with the CPM#1 device.

Study design:

This study is a performance validation pilot with the CPM#1 device that is tested in healthy volunteers. There will only be one study arm, no comparator, and no randomization.

Study population:

35 healthy subjects without signs or symptoms of CECS.

Intervention (if applicable):

Participants will be measured with the CPM#1 device in rest and after a treadmill exercise.

Main study parameters/endpoints:

Inter-observer reliability of the compressibility measured with CPM#1 device.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

Healthy subjects will undergo several compressibility measurements, both before and after a treadmill exercise. They will also complete a NIAPS (Netwerk Inspannings Afhankelijke PijnSyndromen) questionnaire and an 'experience' questionnaire. The harm associated with the CPM#1 device is none. However, the subjects will not benefit from this study.

1. INTRODUCTION AND RATIONALE

Chronic Exertional Compartment Syndrome (CECS) is one of the exercise-induced lower leg pathologies. The prevalence among a general population may be up to 10%[1]. Nevertheless, recognition of CECS by patients and physicians is not optimal[2]. This, on average, causes a delay of 30 months before visiting a surgeon. As a consequence, many patients are unknowingly and undiagnosed forced to stop their sporting activities[3]. As many are military or semi-professional sportsmen, CECS may have a tremendous impact on daily life and career. A subgroup of CECS patients will benefit from a surgical intervention (namely fasciotomy)[2,4]. Recent data suggest that outcome and diagnostic delay are related[5].

Pathophysiology and biomechanics of CECS are not fully understood[6,7]. However, it is generally accepted that CECS is caused by an unusual pressure build-up within a muscle compartment during exertion. This inadequate pressurizing results in diminished vascularisation of the fascia or possibly stretch on the fascia, which consequently results in pressure or traction on nerves and blood vessels causing pain, tightness, cramps, strength loss, or occasionally numbness. Symptoms may occur in four different compartments, namely the anterior-, lateral-, deep posterior- and superficial posterior compartment. The anterior compartment CECS patients (ant-CECS) is mostly affected (40-60%)[3].

To diagnose CECS, a doctor should be alerted by both patient's history (pain, tightness in lower leg muscle) and a physical examination (tender muscle palpation after exercise)[6,7]. If suggestive of CECS, an invasive muscle tissue pressure measurement (intra compartmental pressure measurement, ICPM) of the symptomatic compartment may be advised. This is particularly true as non-invasive treatments for possible CECS were up till then ineffective and a surgical procedure is considered. During this procedure, a catheter is placed into a muscle via a hollow needle using local anaesthesia. The Pedowitz criteria are used for diagnosing CECS. By these criteria, a patient is suffering from CECS if an ICPM in the affected compartment is >15 mmHg during rest, or > 30 mmHg one minute after a provocative exercise, or >20 mmHg after five minutes[8,9].

However, an ICPM is occasionally quite a painful procedure. In addition, there is a small chance of haematoma, infection or nerve damage. Moreover, an ICPM is not flawless in terms of accuracy and a low intra-observer reproducibility was found[10,11]. Large et al[11] showed that, on cadaveric limbs, just 31% of the physicians performing an ICPM used the correct technique. Interestingly, only 60% of these correct measurements were within the five mmHg range of the standard pressure. Vogels et al[10] showed that, of all available ICPM equipment, only the Stryker device and arterial line accurately measured ICPM in a porcine gluteal muscle sample.

Considering these suboptimal test characteristics in non-human models, one could argue that measuring patients will introduce even more variance, especially when, apart from rest measurements, also exercise measurements are involved. Despite these drawbacks, in 2022 an *invasive* ICPM is still considered the 'gold-standard' diagnostic tool for CECS, in the absence of a better one[3].

Over the years, a number of efforts have focused on identifying a reliable *non-invasive* diagnostic technique for CECS[12-15]. A novel tool is possibly provided by measuring tissue compressibility. The idea is that muscle tissue with a high pressure requires more external force to compress to a certain degree compared to tissue with a low pressure. The study device which will be used in this study, the Compremium Compartmental Compressibility Monitoring System (in short, CPM#1 device), is based on this principle[16]. This hand-held ultrasound-based tool measures the distance between various standard landmarks in the lower leg compartment at 10mmHg and at 80mmHg external pressure. The difference in length reflects the compressibility of the compartment (and thus its pressure). The CPM#1 device is non-invasive, not painful, very user friendly, and the measurements can be executed as an 'office procedure' in a couple of minutes. Bench tests with the CPM#1 have shown a good *inter- and intra-observer* reproducibility. An experienced observer, and even an inexperienced observer, were able to produce an inter-observer reliability of 0.945 when applying the same protocol on separate days (Máxima Medical Center, unpublished data). Anwader et al.[16] showed an intra-observer reliability of 0.89 for an experienced and 0.79 for an inexperienced observer with an inter-observer reliability of 0.78.

The present study will focus on determining reliability of the device and its usage in healthy volunteers. At a later stage, it is intended that patients suggestive of having CECS will also undergo these measurements.

2. OBJECTIVES

Primary objective is to validate the *inter-observer* reliability of compressibility measurements with the CPM#1 device during rest.

The secondary objectives are:

- To validate the *intra-observer* reliability of compressibility measurements with the CPM#1 device during rest in healthy volunteers.
- To investigate the effect of exercise on compressibility immediately, one minute, and five minutes after exercise in healthy volunteers.
- To map the invasiveness of the compressibility measurement with the CPM#1 device.

We estimate that for the primary objective and first secondary objective the ICC will be ≥ 0.75 and for the second secondary objective that there will be a difference <2% between compressibility before and after exercise.

3. STUDY DESIGN

A performance validation pilot of the CPM#1 device in healthy volunteers. There will only be one study arm, no comparator, and no randomization. Participants participate in one 60-minute study visit (one session) and no follow-up is planned. The total study duration is three months.

4. STUDY POPULATION

4.1 Population (base)

35 Healthy volunteers recruited among personnel affiliated with Máxima MC.

4.2 Inclusion criteria

- ≥ 18 years
- Proficient in speaking and reading Dutch

4.3 Exclusion criteria

- Presence of complaints suggestive of CECS, previously diagnosed with CECS or previous positive ICPM
- History of surgery or other trauma which penetrated the fascia of the leg
- Other concurrent limb pathologies or anomalies amongst others:
  - Peripheral arterial or venous disease
  - Muscle disorders, diabetes mellitus, peripheral neuropathies
- Unable to exercise for five minutes
- Open wound or painful bruise less than one week ago at site of measurement

4.4 Sample size calculation

As data on this device are scarce, a pragmatic sample size rationale is pursued based on previous studies that were made available to us by the company. Moreover, this study is not aimed at hypothesis testing, rather, we aim to estimate the ICC with certain precision. With the predecessor of CPM#1 it is has been shown that an ICC ≥ 0.75 is achievable and thus demonstrated a good inter-observer reliability.
Measuring the left and right m. tibialis anterior in two directions, an expected ICC = 0.8 (based on bench tests) and a one-sided 95% target confidence interval width of 0.05 based on three observers, a sample size of 140 is required. Since we measure 4 ‘samples’ per participant (each leg the m.tibialis anterior at two different approaches, see section 5.1), we aim to include 35 healthy volunteers (140:4). We do not include dropouts in our calculation since we perform only one 90 minute session without follow-up. Participants who do not complete the

measurements will be replaced for new inclusions, such that we will have a complete data set of 35 participants in the end.

To power for the measurement directly after exercise, using dependent sample T-test with an expected effect size of 0.4 (based on results from bench test), an α of 0.05 and power (β-1) of 0.9, we would require 68 samples. Since the strict timing of the measurements after exercise only allows the measurement of one sample (one compartment using one approach), all participants will undergo two exercise sessions (2x35 = 70).

5. TREATMENT OF SUBJECTS

Healthy subjects are not subjected to any type of treatment besides a lower leg muscle compressibility measurement. A summary of the measurements is given in figure 1.

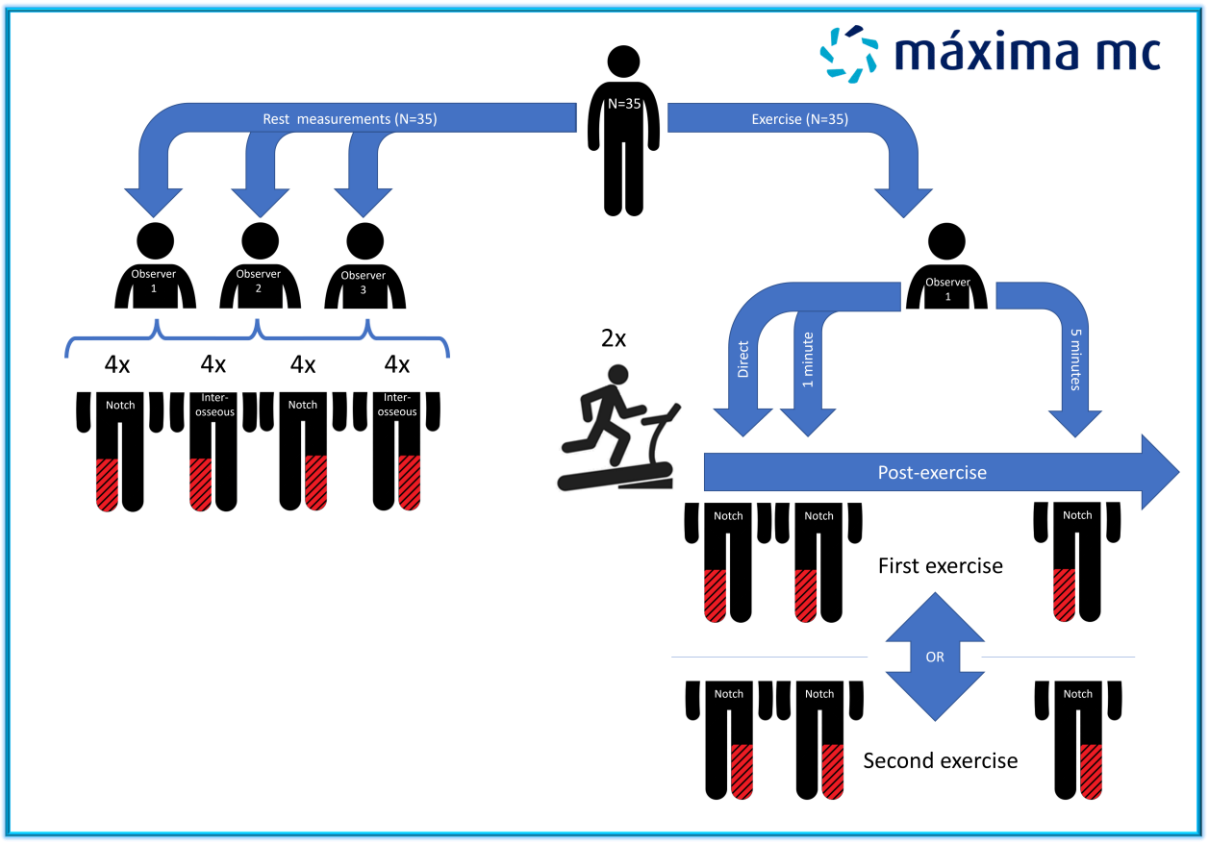


Figure 1: Summary of measurements. A total of 35 healthy volunteers will be included, who all will undergo rest measurements performed by three observers. These three observers will measure the anterior compartment (m. tibialis anterior) four times at four different locations (Right leg with tibial notch as internal landmark, right leg with interosseous membrane as internal landmark, left leg with tibial notch as internal landmark, and left leg with interosseous membrane as internal landmark). All healthy volunteers will then subsequently perform a treadmill exercise twice. After the first time, the right leg with tibial notch as internal landmark will be measured immediately, 1-minute, and at 5-minutes post exercise. After the second exercise the left leg will be measured immediately, at 1-minute, and at 5-minutes post exercise. Randomization will determine whether the right or left leg is measured first.

5.1 Investigational product/treatment

All 35 healthy subjects will undergo four times four measurements in rest (m. tibialis anterior of both legs, using two different internal landmarks). Although the 'tibial notch' between the interosseous membrane and the tibial bone was previously suggested as the optimal landmark[16], recent data from our department suggest that the middle of the interosseous membrane is less variable. These four times four measurements in rest will each be done by three observers.

To measure the effect of exercise, compressibility will be measured immediately, one minute, and five minutes after a standard treadmill exercise at just one leg. The treadmill exercise and the corresponding measurements will be performed twice to include measurements of both legs. The measurements after exercise will be performed by only one observer.

5.2 Use of co-intervention (if applicable)

N.A.

5.3 Escape medication (if applicable)

N.A.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

Compremium Compartmental Compressibility Monitoring System, CPM#1

6.2 Summary of findings from non-clinical studies

For details we refer to the Investigator's Brochure (IB) page 18, chapter 4.

6.3 Summary of findings from clinical studies

For details we refer to the Investigator's Brochure (IB) page 25, chapter 5.

6.4 Summary of known and potential risks and benefits

There are no potential risks known for the CPM#1. Even so there will be no benefits for using the device outside of clinical setting.

6.5 Description and justification of route of administration and dosage

The CPM#1 device is an echo probe; thus, only pressure will be applied on the skin and ultrasound is used.

6.6 Dosages, dosage modifications and method of administration

N.A.

6.7 Preparation and labelling of Investigational Medicinal Product

N.A.

6.8 Drug accountability

N.A.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Inter-observer variance of compressibility among three observers using inter-class correlation coefficients (two-way random effects, single observer, absolute agreement).

8.1.2 Secondary study parameters/endpoints (if applicable)

Intra-observer variance of compressibility within three observers using intra-class correlation coefficients (two-way random effects, single observer, absolute agreement).

Immediate, one minute, and five minutes post-exercise compressibility compared to the oberver's rest measurement compressibility.

8.1.3 Other study parameters (if applicable)

BMI, sex, age, leg dominance, NIAPS questionnaire, Experience questionnaire, internal landmark (notch or interosseous membrane)

8.2 Randomisation, blinding and treatment allocation

Randomisation:
The order of the measurements within a subject will not be completely randomised. However, we will randomize the order of the observers preventing bias due to fixed order of measurement. Also we will randomize the site of measurement where the observer will start (thus left or right leg) and approach (notch or interosseous membrane), by means of an online block randomization tool[17].

Blinding:
Observers will not be blinded to the results (i.e. the compressibility displayed in percentage), as distances cannot be made invisible during determining distances. However, after determining the distances, the device will calculate the CP value itself. Therefore this CP value is not influenced directly by the observer.
Observers will be instructed to not search for the previous measurements performed by previous observers. They are also instructed to not communicate the measurement results among each other.

Treatment allocation:
N.A.

8.3 Study procedures

This outpatient study will be conducted on 35 healthy volunteers. Participants will be placed comfortably in supine position. Measurements of compartment compressibility will be performed for each participant on both legs using the CPM#1. Exercise by means of a treadmill will be performed after all rest measurements have been performed.

Compartments:
Anterior compartment of the leg

Participant positioning:
- Measurement of anterior tibialis compartment
  - Participants will be asked to lie in supine position on an examination table (upper body will be slightly elevated at 5-10°) with a cushion below the head at least 5 minutes before measurement starts.
  - A triangular cushion will be placed below the knee (base width is 28cm, maximum height is 13cm)
  - Heel (with shoes on) will rest on the examination table.

CPM#1 measurements:
- Measurements will be performed according to the workflow depicted and explained in the instructions for use (IFU '20220222_CPM#1_IFU_HVS_E_V1.1' – section 7 and 8), and summarized here below.

Step 1 - Manual investigation
- Identify the compartment for compressibility measurements

Step 2 - Location marking
- Mark the location for compressibility measurements with a medical marker.

Step 3 - Examination with CPM#1
- Place the probe on the target area
- Identify correct landmark
- Compress the compartment
  - Increase steadily the pressure applied by the CP probe to 80 mmHg.

Step 4 - Settings landmarks
- Set the outer and inner landmark of the 10mmHg-picture and 80mmHg-picture

Exercise:
- Participants will walk on a treadmill with standardized walking speed (5.0 km/hour) and slope (15%) for 5 minutes.

- Participants will then walk towards the bench and position themselves accordingly to previous anterior compartment measurements.
- Immediate, one minute, and five minutes post-exercise CPM#1 measurements will be performed at one leg.
- Exercise and post-exercise CPM#1 measurements will be repeated for the other leg.

Questionnaires

NIAPS questionnaire:

- Baseline (full questionnaire as appendix, *'F1-NIAPS Baseline'*) with one additional question about leg dominance.

Experience questionnaire:

- Score 1-5 (full questionnaire as appendix, *'F1-Ervaringsvragenlijst v1.0'*) questioning the intensity, how painful, the nuisance, the duration of the study and the non-invasive pressure measurements.

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)

N.A.

8.5 Replacement of individual subjects after withdrawal

Measurements will only take place during one 90-minute session, thus there will be no withdrawal after data is collected. If participants withdraw before or during measurements, these participants will be replaced.
If for some reason more than one repetition is missed in one category, or one observer is missing, for that specific analysis this data will be excluded.

8.6 Follow-up of subjects withdrawn from treatment

N.A.

8.7 Premature termination of the study

It is not expected that adverse events will happen that will result in premature termination of the study. Though the study might be terminated prematurely when:

- An agency's (for example METC) approval is withdrawn
- The department withdraws the study
- If inclusion of patients is disturbed due to unforeseen circumstances

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. However, as no medication will be used, and no further invasive measurements are performed, we expect no adverse events from the device. Potential adverse events that might occur during treadmill exercise are: Dyspnea, falling accidents, and exhaustion.

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 investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs: Non excluded.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within seven days of first knowledge for SAEs that result in

death or are life threatening followed by a period of maximum of eight days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum fifteen days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

N.A.

9.3 Annual safety report

N.A.

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

N.A.

10. STATISTICAL ANALYSIS

Intra-class correlation coefficients will be calculated as indicated below and described using 95% confidence intervals.

10.1 Primary study parameter(s)

The primary endpoint of inter-observer variability will be the intraclass correlation coefficient (ICC) of agreement between three observers, four sites per subject, and four repetitions per measurement. The ICC will be assessed using a two-way random effects model. Both observers and subjects will be included as random effects. The first measurement for each location will be taken from every observer to calculate the ICC. Apart from that, the ICC will be measured using the average of the four repetitions of ratings, to estimate the effect on the ICC of repetitive measurements. “Good reliability” classification will be reached if the lower bound of the computed ICC confidence interval does not fall below 0.75.

10.2 Secondary study parameter(s)

The secondary endpoint of intra-observer variability will be the intraclass correlation coefficient (ICC) of agreement within three observers, four sites per subject, and four repetitions per measurement. The ICC will be assessed using a two-way random effects model. Both subjects and repetitions will be included as random effects. The repeated measures will be analysed for each observer separately and this agreement serves to address differences between observers. “Good reliability” classification will be reached if the lower bound of the computed ICC confidence interval does not fall below 0.75

The second secondary endpoint is the comparison between post-exercise (immediate, one minute, and five minutes) compressibility and rest compressibility. This will be analysed using a dependent sample t-test.

10.3 Other study parameters

Additional secondary analyses (exploratory analyses) of outcomes not foreseen in this protocol may be undertaken to explore additional features of the performance, acceptability and safety of the CPM#1 device. Where possible these will be specified in the pre-defined statistical analysis plan.

10.4 Interim analysis (if applicable)

N.A.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

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

11.2 Recruitment and consent

Healthy volunteers will be recruited by the coordinating investigator among personnel of Máxima MC.

There will be several ways to recruit healthy volunteers:

- Presentation during the 'Inspiratielunch' at MMC
- Flyer distribution at the MMC restaurant and in meeting rooms after obtaining approval from the corresponding department.

When interested, the healthy volunteers will receive the patient information flyer via e-mail or by post. After one week, the coordinating investigator will contact the volunteer to ask whether he/she would be willing to participate. If more time to consider is required, or unable to reach the healthy volunteer, after another week the coordinating investigator will contact the volunteer again.

11.3 Objection by minors or incapacitated subjects (if applicable)

N.A.

11.4 Benefits and risks assessment, group relatedness

Healthy volunteers will have no direct benefits of this study.

11.5 Compensation for injury

N.A.

11.6 Incentives (if applicable)

N.A.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

First and foremost, subject relatable information as date of birth, name and contact information will be stored in a key file (excel). This file is stored in a folder on the MMC server which is only accessible by personnel directly involved in the study. The Key file is password protected, only the PI and coordinating investigator know this password.
Healthy volunteers will be coded as: HVMMC_001 / 002 / 003 / 004
In the study databases (Research Manager) these codes will be assigned to each participant. Results and questionnaires will be filled out on paper during the measurement session. Hereafter the data will be manually transferred to the database. Paper will be stored in a locked room with locked closet and stored for 5 years.

12.2 Monitoring and Quality Assurance

Monitoring will be performed by Clinical Trial Centre Maastricht (CTCM). After approval of the protocol, a monitoring plan will be made together with CTCM.

12.3 Amendments

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

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 sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. 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 and the competent authority 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 and the Competent Authority.

12.6 Public disclosure and publication policy

The data gathered from this research will be used for a publication. There is an agreement between subsiding party and investigator that data will be shared anonymously as the subsiding party might be able to use this data for improving their product and/or gaining certain certifications. The subsiding party is not allowed to use the data in another fashion that would result in a publication.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

The CPM#1 device is an echo probe, therefore the level of knowledge is: fully understood.

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

The producers of the device (CPM#1) have shown in several bench test and in an usability study that the device can be used safely in humans. The evaluation consisted of an observational study with 15 healthcare professionals were asked to perform two measurements.

Further Sellei et al[15] has used the CPM#1 predecessor (VeinPress device) in six patients with elevated intracompartmental pressure to determine feasibility of muscle elasticity measurements.

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

N.A.

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

N.A.

e. Analysis of potential effect

N.A.

f. Pharmacokinetic considerations

N.A.

g. Study population

The research subjects in the studies are healthy volunteers not suffering from CECS or other limb anomalies or pathologies.

h. Interaction with other products

Not expected

i. Predictability of effect

No effects expected

j. Can effects be managed?

No effects expected.

13.2 Synthesis

There is no additional risk effect for the CPM#1 device expected. The device has already been considered safe to be used by the department 'klinische fysica'/'technische dienst'. Therefore, the burden of the CPM#1 device is close to nothing and it is acceptable for the subjects to undergo these measurements.

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