University of Applied Sciences and Arts of Southern Switzerland
Department of Business Economics, Health and Social Care

SUPSI

Originally in German, translated into English

Clinical Investigation Plan (CIP)

A randomized, controlled trial to investigate the effectiveness of cryotherapy with intermittent dynamic compression after total knee arthroplasty

Intermittent compression and cryotherapy after total knee arthroplasty

Type of investigation:	Clinical investigation concerning medical devices (MD).
Categorisation:	Category according to Art 6 ClinO-MD (A1).
Registration:	SNCTP (follows) Clinicaltrials.gov NCT05395273
Identifier:	2022-D0056
Principal Investigator and Sponsor, or SponsorInvestigator:	University of Applied Sciences and Arts Southern Switzerland Department of Business Economics, Health and Social Care Physiotherapy Graubünden Weststrasse 8 7302 Landquart +41 81 300 01 70 Contact / Director of Studies Clijsen Ron, PhD University of Applied Sciences and Arts Southern Switzerland Physiotherapy Graubünden Weststrasse 8 7302 Landquart +41 81 300 01 75 ron.clijsen@supsi.ch
Sponsor representative (if the Sponsor is not located in Switzerland)	Thim van der Laan AG Thim van der Laan jr. Weststrasse 8 / CH- 7302 Landquart
Medical Device:	The Game Ready GR PRO 2.1 is a certified medical device that complies with European regulations, directives and standards (93/42/EEC, EN60601-1, EC 60601-1-2, CE 0086).

CIP Version and Date:	Version 2 (21.06.2022)

CONFIDENTIAL

Signature Page(s)

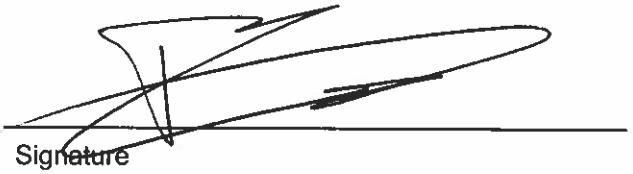
ID number of the investigation:	*2022-D0056*
Title:	*Eine randomisierte, kontrollierte Studie zur Untersuchung der Effektivität von Kryotherapie mit intermittierend dynamischer Kompression nach Knie-Totalendoprothetik*

The Sponsor, the Principal Investigator and the Statistician have approved the CIP version 02 (dated 21.06.2022) and confirm hereby to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, ICH-GCP as far as applicable, and the local legally applicable requirements.

Sponsor: Thim van der Laan junior

Landquart, 08.07.2022

Place/Date



Signature

Principal Investigator: *Ron Clijsen, PhD*

Landquart, 08.07.2022

Place/Date

Signature

Principal Investigator at the local investigational site:

I have read and understood this CIP version 02 (dated 21.06.2022), and agree to conduct the investigation according to the CIP, the current version of the World Medical Association Declaration of Helsinki, ISO14155 norm, ICH-GCP as far as applicable, and the local legally applicable requirements.

Site:	*Regionalspital Surselva AG*
Principal investigator at the local investigational site:	*Dr. med. Martin Wonerow* Dr. med. Martin Wonerow Chefarzt Orthopädie Facharzt für Orthopädie/Traumatologie (CH) Spez. Sportmedizin (SGSM) Expertenzertifikat Fusschirurgie (GFFC e.V.) Zertifizierter Fusschirurg (D.A.F. und GFFC e.V.) Manuelle Medizin (MWE) Regionalspital Surselva AG 7130 Ilanz
Ilanz, 07.07.2022	
Place/Date	Signature

Site:	*Regionalspital Surselva AG*
Investigator at the local investigational site:	*Dr. med. Sebastian Ulsamer* Dr. med. Sebastian Ulsamer Leiternder Arzt Orthopädie Facharzt Orthopädische Chirurgie/Traumatologie Schwerpunkt Sportmedizin SGSM und ÖÄK Basiszertifikat Fusschirurgie GffC Regionalspital Surselva AG 7130 Ilanz
Ilanz, 07.07.2022	
Place/Date	Signature

Table of Contents

SYNOPSIS

Sponsor / SponsorInvestigator	Sponsor: Thim van der Laan AG Thim van der Laan jr. Weststrasse 8 / CH- 7302 Landquart Investigator: University of Applied Sciences and Arts Southern Switzerland (SUPSI) Department of Business Economics, Health and Social Care Physiotherapy Graubünden Attn: Ron Clijsen, PhD Weststrasse 8 CH-7302 Landquart
Title:	A randomized, controlled trial to investigate the effectiveness of Cryotherapy with intermittent dynamic compression after kneeTotal arthroplasty
Short title / Investigation ID:	Intermittent compression and cryotherapy after total knee arthroplasty
Clinical Investigation Plan, version and date:	Version 02 – 21.06.2022
Registration:	*SNCTP* (follows) Clinicaltrials.gov NCT05395273
Category and its rationale:	Category according to Art 6 ClinO-MD (A1).
Name of the MD, Unique Device Identification (UDI), name of the manufacturer	The Game Ready GR PRO 2.1 is a certified medical device that complies with European regulations, directives and standards (93/42/EEC, EN60601-1, EC 60601-1-2, CE 0086). The system can administer ice-free cold treatment (5-13°C), with or without intermittent pneumatic compression treatment (5-75 mmHg). It is a closed system (device and pressure cuff) and is therefore hygienic and safe to use in the clinic. The device is already being used in several Swiss clinics and institutions.
Stage of development:	Step 5: Product launch and postlaunch assessment

Background and rationale:	The rehabilitation process after surgery is characterized by pain, swelling and inflammation in the perioperative tissues. This also applies after total knee endoprosthesis (TKA), as pain, swelling and inflammation are promoted due to the high concentration of nerve endings, the amount of bone resection, and bleeding in a closed space (joint capsule). These factors can complicate the prescribed postoperative physical therapy program for mobilization. Consequently, the patient's functional abilities are compromised with postoperative pain, swelling, and inflammation and can affect the final outcome. Compression and cryotherapy are traditionally used in postoperative recovery from TKA to mitigate these factors. Compression is believed to reduce edema by increasing hydrostatic pressure, thereby promoting the outflow of fluid into the interstitial space. Cold therapy can reduce the migration of leukocytes and slow down the transmission of nerve signals, resulting in a reduction in inflammation and having a short-term analgesic effect (Su et al. 2012). One study speaks of similar effects of cold compression bandages in simple arthroscopy, anterior cruciate ligament reconstruction and total arthroplasty (Thienpont 2014). Increased clearance is thought to lower inflammatory mediators, which often lead to edema and pain. In addition, physical pressure on hypertonic surrounding soft tissues and mechanical stretching of the contractile component of the muscles can improve tissue tension, which can potentially lead to a further reduction in edema and pain (Ebert et al. 2013). Game Ready is a medical product that, according to the manufacturer, provides faster, deeper penetrating and longer-lasting cooling with a dual function (pneumatic compression and continuous cold delivery). The cooling and intermittent compression is not permanent, but controlled (by a controller) in sessions of 30 minutes. After 30 minutes, the system switches to standby mode for 30 or 60 minutes. Thus, the processes important for healing are not suppressed and the tissue is not damaged by too intensive cooling. The healing processes are controlled (unnecessary swelling and pain reduced) and optimally supported thanks to intermittent compression (the tissue is supplied with fresh blood, oxygen and nutrients and inflammation-based waste products are removed via the lymphatic system. At the moment, there are still few studies in the literature that have investigated the effect of cryotherapy with intermittent dynamic compression with Game Ready after total knee arthroplasty (Su et al. 2012; Leegwater et al. 2012; Waterman et al. 2012; Murgier and Cassard 2014; Klaber, Greeff, and O'Donnell 2019; Nabiyev et al. 2018; Bellon et al. 2019). Further randomized, controlled trials are needed to investigate the effect of cryotherapy with intermittent dynamic compression.

Objective(s):	In this study, the effect of repeated cold application with dynamic compression with the Game Ready and a control group will be investigated. The influence of these interventions and their effects will be investigated after a total knee endoprosthesis operation has been performed during the hospital stay. The change in the following parameters is examined: questionnaire on everyday activity and patient satisfaction, joint circumference in mm, skin temperature in C°, range of motion in degrees, morphine consumption in number per day, Pain sensation with the VAS, the length of the days of stay, the 10-meter walking test and the timed up-and-go in seconds. The aim is to determine the effects of cold application with dynamic compression in order to be able to make recommendations. The current scientific knowledge requires further studies to substantiate or refute effects that have already been established.
Outcome(s):	Primary outcomes -Questionnaire Everyday Activity [Score] -Patient satisfaction [cm] -Joint circumference [mm] -Range of motion [degrees] -Skin temperature [°C] -Morphine consumption [number] - Visual analog pain scale [cm] -Duration of stay [days] -10-meter walk test[s] -Timed-Up-and-Go [s]
Design:	Randomized, controlled trial

Inclusion / exclusion criteria:	Inclusion Criteria: • Signed Informed Consent by the participant • Diagnosed gonarthrosis • Planned implantation of a primary total knee endoprosthesis by the Regional Hospital Surselva AG Exclusion criteria: • Decompensated hypertension in the affected area • Acute inflammatory phlebitis in the affected area • Patients with acute paroxysmal cold hemoglobinuria, or cryoglobulinemia • significant vascular disorder in the affected area (e.g., due to previous frostbite, significant atherosclerosis, diabetes, or ischemic vascular disease) • History of pulmonary embolism or risk factors for deep vein thrombosis or pulmonary embolism in the affected area • No increased venous or lymph reflux in the affected leg is desirable due to e.g. by carcinoma • Raynaud's disease • Hypersensitivity to cold • Fear of cold/compression
Measurements and procedures:	Recruitment: The subject information and declaration of consent are sent to the Subjects during the preoperative consultation with Dr. med. Martin Wonerow, Regionalspital Surselva AG, Spitalstrasse 6, CH7130 Ilanz. Questions may be asked. If the test subjects agree with the information, they are called up for the first screening. This includes the explanations, the signature of the declaration of consent, and the completion of the health questionnaire. If all the criteria of the inclusion and exclusion criteria are met, the subject will be included in the study.

Intervention:	The Game Ready GR PRO 2.1 is a certified product that complies with European regulations, directives and standards. The system can administer ice-free cold treatment and intermittent pneumatic compression treatment, providing healthcare professionals with options for different patients, procedures, injuries and rehabilitation stages. The following intervention is performed according to the manufacturer's protocol for patients with primary total knee arthroplasty: 48 hours after the The operation starts the Game Ready Intervention, if tolerable, with little compression (level 1 = 5-15 mmHg) and cooling at the coldest level tolerable by the participant (corresponds to program 2). The cooling should be perceived as "pleasant" by the participant. The intervention lasts one hour, of which 30 minutes are on and 30 minutes off cycles. The on cycle includes the duration of the intervention (cooling and compression), while the off cycles include the rest period. After 60 minutes, the device is removed. If compression is not tolerated, it can also be omitted (corresponds to program 1). The intervention is performed twice a day for the first four days after surgery. The coldest tolerable temperature level is determined anew with each treatment. The compression level can be increased depending on the participant. Medium compression may only be applied from the second day onwards (corresponds to programme 3).
Control intervention (if applicable):	In order to obtain high-quality study results, the test subjects are exposed to only one experimental condition at a time. There are two groups. In order to maintain the quality of the study, a randomized controlled trial design will be chosen. The division into the groups is randomized. The data collected in this way is pooled by outcome or group. The control group will receive ordinary physiotherapy treatment, without Game Ready application.
Number of subjects with rationale:	n=28 (14 per group) G-Power analysis: effect size at 0.8
Duration of the investigation:	May 2022 – December 2024
Investigation schedule:	May 2022- subject –In (planned) June 2023- subject –Out (planned)

Investigator(s):	Examiner: Ron Clijsen, PhD 1,2,3 Hohenauer Erich, PhD 1,2,3 Friday Livia 2 Herten Miriam 2 Bianchi Giannina 2 Elke Pollock 2 1 University College Physiotherapy Thim van der Laan, Weststrasse 8, 7302 Landquart 2 University of Applied Sciences and Arts Southern Switzerland, Rehabilitation and Exercise Science Laboratory (RESlab), Department of Business Economics, Health and Social Care, Physiotherapy Graubünden, Weststrasse 8, 7302 Landquart 3 Vrije Universiteit Brussels, Faculty of Physical Education and Physical Therapy, Pleinlann 2, 1050 Brussels Contact / Principal Investigator: Clijsen Ron, PhD University of Applied Sciences and Arts Southern Switzerland Physiotherapy Graubünden Weststrasse 8 7302 Landquart +41 81 300 01 75 ron.clijsen@supsi.ch
Investigational Site(s):	Single-centric investigation: Regionalspital Surselva AG Spitalstrasse 6 CH-7130 Ilanz
Statistical considerations:	Repeated measure ANOVA Two-way Bonferroni correction Factors: -Task -Time The significance level is set at $p<0.05$, and the statistical data analysis is carried out with SPSS.
Compliance statement:	This investigation will be conducted in compliance with the CIP, the current version of the Declaration of Helsinki, ISO14155, ICH-GCP (as far as applicable) as well as all national legal and regulatory requirements.

ABBREVIATIONS

AE	Adverse Event
GOODBYE	Adverse Device Effect
ASADE	Anticipated Serious Adverse Device Effect
ASR	Annual Safety Report

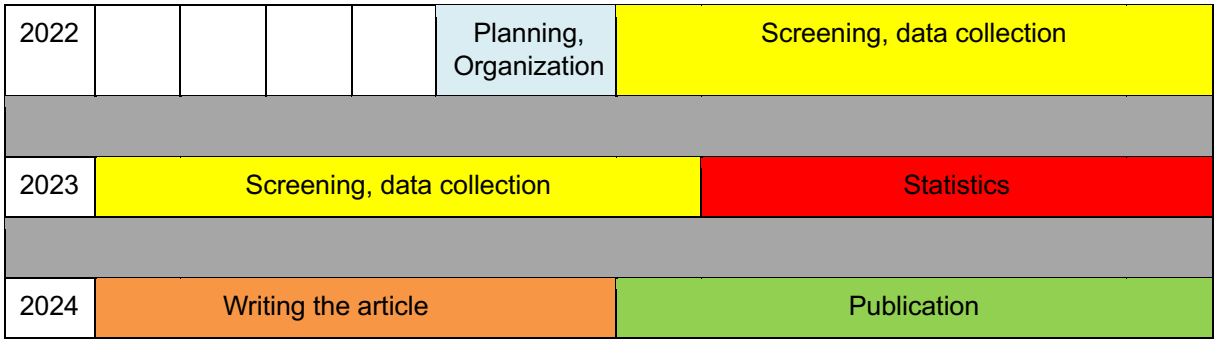
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CIP	Clinical investigation plan
ClinO	Ordinance on Clinical Trials in Human Research *(in German KlinV, in French Oclin, in Italian OSRUm)*
ClinO-MD	Ordinance on Clinical Trials with Medical Devices *(in German: KlinV-Mep, in French: Oclin-Dim, in Italian: OSRUm-Dmed)*
CRF	Case Report Form (pCRF paper CRF; eCRF electronic CRF)
DD	Device Deficiency
DMC / DSMC	Data Monitoring Committee, Data Safety Monitoring Committee
Ho	Zero hypothesis
H1	Alternative hypothesis
HRA	Federal Act on Research involving Human Beings *(in German: HFG, in French: LRH, in Italian: LRUm)*
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonisation – guidelines of Good Clinical Practice
IFU	Instruction For Use
ISF	Investigator Site File
ISO	International Organisation for Standardisation
ITT	Intention to treat
MedDO	Medical Devices Ordinance *(in German: MepV, in French: Odim, in Italian: Odmed)*
MD	Medical Device
MDR	Medical Device Regulation (EU) 2017/745 of 5 April 2017
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SDV	Source Data Verification
SNCTP	Swiss National Clinical Trials Portal
SOP	Standard Operating Procedure
USADE	Unanticipated Serious Adverse Device Effect

SUMMARY OF THE REVISION HISTORY IN CASE OF AMENDMENTS

Version Nr, Version Date	Chapter	Description of change	Reason for the change
01	-	-	-

INVESTIGATION SCHEDULE

	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Head


2022
Planning, Organization
Screening, data collection
2023
Screening, data collection
Statistics
2024
Writing the article
Publication

1. INVESTIGATION ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator

Thim van der Laan AG
Weststrasse 8
7302 Landquart

Thim van der Laan jr.
+41 81 300 01 70
t.vanderlaan@physioschule.ch

1.2 Principal Investigator(s)

University of Applied Sciences and Arts Southern Switzerland
Department of Business Economics, Health and Social Care
Physiotherapy Graubünden

Ron Clijsen, PhD
Weststrasse 8
7302 Landquart +41
81 300 01 75
ron.clijsen@supsi.ch

1.3 Statistician ("Biostatistician")

University of Applied Sciences and Arts Southern Switzerland
Department of Business Economics, Health and Social Care
Physiotherapy Graubünden

Erich Hohenauer, PhD
Weststrasse 8
7302 Landquart +41 81
300 01 75
erich.hohenauer@supsi.ch

1.4 Research laboratory

Ron Clijsen, PhD ron.clijsen@supsi.ch

Hohenauer Erich, PhD erich.hohenauer@supsi.ch

Friday Livia livia.freitag@supsi.ch

Herten Miriam
miriam.herten@supsi.ch
Giannina Bianchi
giannina.bianchi@supsi.ch

Elke Pollock
polloelk@students.zhaw.ch

Weststrasse 8
7302 Landquart
+41 81 300 01 75

1.5 Monitoring institution

Vrije Universiteit Brussels
Faculty of Physical Therapy
Prof. Peter Clarys, PhD

Pleinlaan 2 1050
Brussels
peter.clarys@vub.ac.be

1.6 Data Safety Monitoring Committee

All data obtained from the study participants will be encoded and not passed on to other people. Personal data and personal details are stored in paper form in a locked filing cabinet. Only the study supervisor, the head of the research laboratory and the study director at the same time have access here, with the management of the documents being the responsibility of the head of the research laboratory.

All digital data is encoded. No conclusions can be drawn about individuals. The digital data is stored and archived on internal computers and is not released to outsiders.

Employees involved in data processing have no insight into the personal data and the coding of it.

1.7 Any other relevant Committee, Person, Organization, Institution

Regionalspital Surselva AG
Dr. med. Martin Wonerow
Spitalstrasse 6
CH-7130 Ilanz
m.wonerow@spitalilanz.ch

Regionalspital Surselva AG
Dr. med. Sebastian Ulsamer
Spitalstrasse 6
CH-7130 Ilanz
s.ulsamer@spitalilanz.ch

The study is being led and coordinated by the University of Applied Sciences and Arts Southern Switzerland, Physiotherapy Graubünden, Weststrasse 8, CH7302 Landquart, in the research laboratory of the research group, which is officially called the Rehabilitation and Exercise Science Laboratory (RESlab).

The study is being carried out at the Regional Hospital Surselva AG, Spitalstrasse 6, CH-7130 Ilanz. The test product and all measuring equipment are stored in the orthopaedics department. The measurements are taken in a room prepared for this purpose. The applications with the test product are carried out in the hospital room of the test subjects.

The mentioned sponsor, Thim van der Laan AG, is responsible for the management according to KlinV §2c.

As far as is known, no further studies with this order are taking place in the institutions mentioned (University of Applied Sciences and Arts of Southern Switzerland and Regional Hospital Surselva AG, Spitalstrasse 6, CH-7130 Ilanz).

Table 1 - Summary of responsibilities and tasks

Range	Sponsor	Inspector
Responsibilities	Management Financing Responsibility of the study	Management, coordination, practical implementation in the Sponsor's mission
Compensation for the Inspectors	-	No further compensation planned
Privacy	Responsible for the Compliance with data protection	Adopts the Sponsor's order regarding the Privacy
Data ownership	Responsible and disposes of the data	-
Publication	-	Takes over the work steps of the publication on behalf of the sponsor

2. ETHICAL AND REGULATORY ASPECTS

The final positive decision of the CEC on the conduct of the investigation will be made and given in writing to the Sponsor before the investigation can start. Additional requirements set by the authorities must be implemented.

2.1 Registration of the investigation

The study is registered under the following two registries:

- SNCTP (follows, date xx.xx.xxxx)

-Clinicaltrials.gov (NCT05395273, Date 18.05.2022)

2.2 Categorisation of the investigation

The study falls under the following category:

Category A clinical trial, subcategory A1.

Reason: no other invasive or otherwise stressful procedures are examined in the study or are the content of the study. The medical device under investigation is CE marked, is used in accordance with the instructions for use and is not prohibited in Switzerland (Art. 6 para. 1 KlinVMep).

2.3 Competent Ethics Committee (CEC)

The Sponsor-Investigator will submit the investigation to the CEC and obtain ethical committee approval before the start of the investigation. The PI ensures that approval from the CEC is obtained and filed in the Investigator site file before the investigation starts.

2.3.1 Reporting duties to the Competent Ethics Committee

Amendments are reported according to Art. 15 ClinO-MD (see also 2.10).

The regular or premature end of the investigation as well as the interruption of the investigation is reported to the CEC within 15 days (within 24 hours if it is due to security reasons) (Art. 36 ClinO-MD). The reasons for a premature end or an interruption have to be explained.

A final report shall be submitted within one year after the regular end of the investigation and within 3 months after a premature end of the investigation (Art. 37 ClinO-MD).

2.4 Ethical Conduct of the Investigation

The investigation will be carried out according to the CIP and with principles enunciated in the current version of the Declaration of Helsinki, the European Regulation on medical devices 2017/745 (MDR), the Norms ISO14155 and ISO14971, the ICH-guidelines of Good Clinical Practice (GCP) as applicable, the Swiss Human Research Act (HRA) and its Ordinances and Swiss regulatory authority's requirements. The CEC will receive the Annual Safety Report (ASR) and interim reports and be notified about investigation stop/end in agreement with local requirements.

2.5 Declaration of interests

There is no financial conflict of interest on the part of the sponsor/investigator, nor is there a corresponding relationship of dependency.

2.6 Patient Information and Informed Consent

The PI explains to each subject the nature of the investigation, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each subject is informed that the participation in the investigation is voluntary and that he/she may withdraw from the investigation at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment. The subjects are informed that he/she can ask any question, and consult with family members, friends, their treating physicians or other experts before deciding about their participation in the investigation. Enough time is given to the subjects.

The subjects are informed that authorised individuals other than their treating physician may examine his/her medical records.

All subjects a given a subject information sheet and a consent form describing the investigation and providing sufficient information for the subjects to make an informed decision about their participation in the investigation.

The formal consent of a subject, using the approved consent form, is obtained before the subject is submitted to any investigation procedure.

The subject should read, understand, and voluntarily agree before signing and dating the informed consent form, and is given a copy of the signed document. The consent form is signed and dated by the subject and the PI (or her/his designee). The signed consent form it is retained as part of the investigation records.

2.7 Subject privacy and confidentiality

The Sponsor and the PI affirm and uphold the principle of the subjects' right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the subjects shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this investigation is considered confidential and disclosure to third parties is prohibited.

For data verification purposes, authorised representatives of the Sponsor, the CEC may require direct access to parts of the medical records relevant to the investigation, including subjects' medical history.

All data obtained from the study participants will be encoded and not passed on to other people. Personal data and personal details are stored in paper form in a locked filing cabinet. Only the study supervisor, the head of the research laboratory and the study director at the same time have access here, with the management of the documents being the responsibility of the head of the research laboratory.

All digital data is encoded. No conclusions can be drawn about individuals. The digital data is stored and archived on internal computers and is not released to outsiders.

Employees involved in data processing have no insight into the personal data and the coding of it.

2.8 Early termination of the investigation

The Sponsor may terminate the investigation prematurely according to certain circumstances, for example:

- ethical concerns,
- insufficient subject recruitment,
- when the safety of the subjects is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of the investigation unwise,
- early evidence of benefit or harm of the experimental intervention.

2.9 Clinical investigation plan amendments

Substantial amendments are only implemented after approval by the CEC (Art. 15 ClinO-MD). The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR).

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of the subjects may proceed without prior approval by the Sponsor and the CEC. Such deviations shall be documented and reported to the Sponsor and the CEC within 2 days (Art. 34 ClinO-MD).

All non-substantial amendments are communicated to the CEC together with the Annual Safety Report (ASR) (Art. 15 ClinO-MD). The ASR shall include any deviations from the CIP that may have affected the rights, safety or well-being of the subject or the scientific integrity of the investigation (ISO14155).

2.10 Deviation from the Clinical Investigation Plan

The use of waivers from the CIP is prohibited (Annex XV, Chapter 2, Art. 3.10 MDR).

Adjustments and changes to the current study are only permissible after review by the CEC.

Short-term (non-substantial) changes to the protocol prior to an audit by the CEC may be made to ensure the rights and safety of participants. However, such adjustments must be documented and reported to the CEC with the annual safety report (Art. 15 para. 5 ClinO-MD).

Significant changes are only permissible after a review of the CEC. Any other changes must be notified to the CEC as soon as possible and listed in the annual report.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale for the clinical investigation

Recovery after surgery is characterized by pain, swelling, and inflammation in the perioperative tissues. This also applies after total knee endoprosthesis (TKA). Due to the high concentration of nerve endings, the amount of bone resection and bleeding in a closed space (joint capsule), pain, swelling and inflammation are promoted. These factors can complicate the prescribed postoperative physical therapy program for mobilization. Consequently, the patient's functional abilities are compromised with postoperative pain, swelling, and inflammation and can affect the final outcome. Compression and cryotherapy have traditionally been used in the postoperative treatment of TKA to mitigate these factors. Compression is believed to reduce edema by increasing hydrostatic pressure, thereby promoting the outflow of fluid into the interstitial space. Cold therapy can reduce leukocyte migration and slow down the transmission of nerve signals, resulting in a reduction in inflammation and having a short-term analgesic effect (Su et al. 2012).

One study showed similar effects of cold compression bandages in simple arthroscopy, anterior cruciate ligament reconstruction and total arthroplasty (Thienpont 2014). The authors also mentioned other applications of cryotherapy, including first-generation cryotherapy with crushed ice in a plastic bag, cold or gel packs; Second-generation cryotherapy with circulating ice water with or without compression such as Cryo/Cuff (Aircast, Vista, CA, USA) or Game Ready (CoolSystems Inc, Concord, CA, USA); and advanced third-generation computerized devices with continuous controlled cryotherapy (cTreatment, Waegener, Beerse, Belgium; and CTM 5000, Ener-C AG, Baar, Switzerland).

Game Ready GR PRO 2.1 is a medical product that provides faster, deeper penetrating and longer-lasting cooling with dual function (pneumatic compression and continuous cold delivery) and the cuff construction with maximum body contact. The cooling and intermittent compression in Game Ready is not permanent, but optimized (by a control) in sessions of 30 minutes. After 30 minutes, the system switches to standby mode for 30 or 60 minutes. Thus, the processes important for healing are not suppressed and the tissue is not damaged by too intensive cooling. The healing processes are optimized (swelling and pain are reduced) and supported thanks to intermittent compression. The tissue is supplied with blood, oxygen and nutrients and inflammation-based waste products are transported away via the lymphatic system (MTR 2021). The additional compression in the form of pressure on hypertonic surrounding soft tissues and the mechanical stretching of the contractile component of the muscles improve tissue tension, which can potentially lead to further improvement of edema and pain (Ebert et al. 2013).

At the moment, there are only a few studies in the literature that have investigated the effect of cryotherapy with intermittent dynamic compression with Game Ready after total knee arthroplasty.

Aim of the study

In this project, the effect of repeated cold application with dynamic compression with the Game Ready and a control group will be investigated. The influence of these interventions and their effects will be investigated after a primary total knee endoprosthesis operation during the hospital stay. The change in the following parameters is examined: questionnaire on everyday functions and patient satisfaction, joint circumference in mm, range of motion in degrees, skin temperature in C°, morphine consumption per day, pain perception with the VAS, the 10-meter walk test, timed-up-and-go and the length of the days of stay.

The aim is to determine the effects of cold application with dynamic compression in order to be able to make recommendations. The current scientific knowledge requires further studies to substantiate or refute effects that have already been established.

3.2 Identification and description of the Investigational Medical Device

The Game Ready GR PRO 2.1 builds on the groundbreaking Game Ready technology and is a multimodality recovery device for professional users. The system can deliver ice-free cold treatment and intermittent pneumatic compression treatment, providing healthcare professionals with flexible options for different patients, procedures, injuries and rehabilitation stages.

Established principles such as PECH (pause, ice, compression, elevation) can be taken to a new level with the state-of-the-art Game Ready GR PRO 2.1. Cumbersome procedures for contrast treatment will be simplified with the compact, practical device. In addition, these can be monitored and controlled more consistently than conventional methods.

The unit consists of the following parts: the GRPro 2.1 control unit, connecting hose, the wrap (sleeve and heat exchanger), power supply and cable (see Figure 1). Only the cuff comes into contact with the patient's skin (see also Figure 2, right). The device is controlled via a touchscreen computer interface on the control unit. The user can choose between different treatment modalities and easily change and monitor the settings for treatment duration, temperature and compression. The double-acting (cryotherapy and compression) and anatomically designed Game Ready cuffs can be used specifically for specific parts of the body.

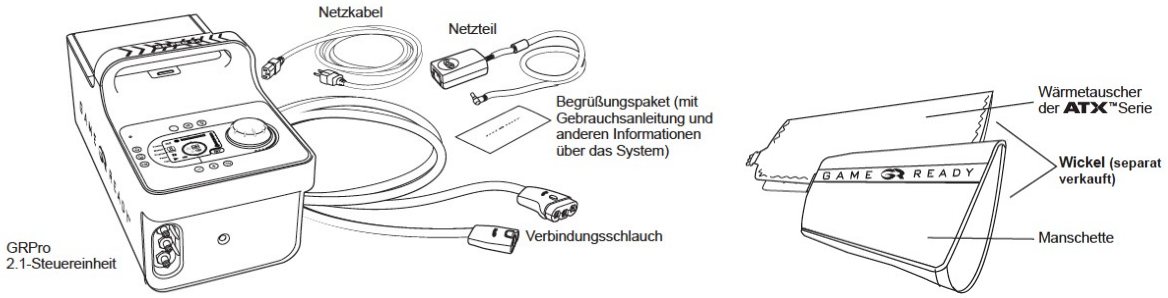


Figure 1 - Game Ready GR PRO 2.1 (https://gameready.com/gr-pro-cold-therapy-unit/)

This device is used for the treatment of post-traumatic, post-operative (medical and/or surgical) and acute injuries, as well as for the reduction of edema, swelling and pain when cold and compression are indicated.

According to the manufacturer, the following foreseeable serious adverse events and product defects may occur:

-tissue damage due to improper or too long use than described by the manufacturer,

-burning, itching, increasing swelling, pain, blisters, increasing redness, discoloration and other visible changes during treatment,

-Change in wound conditions (if the wrap is not applied over the bandage or clothing),

-Risk of electric shock (if other power supplies are used, housing parts are removed, or damaged cables and connecting hoses are used) and

-Device damage (if there is no or too hot water in the ice box, the device is lifted up by the lid, or wraps from other manufacturers have been used).

Despite the points listed above, the risk is classified as minimal, as no serious events can occur if used correctly and observed during application.

The following contraindications must be observed:

-patients with acute inflammatory phlebitis in the affected area,

-Patients with a history of or risk factors for deep vein thrombosis or pulmonary embolism in the affected area to be treated (including long periods of bedriddenness), -Patients with significant atherosclerosis or other ischemic vascular disease in the affected area,

-Patients with a condition in which increased venous or lymphatic reflux in the affected arm or leg is not desired (e.g. carcinoma),

-Patients with significant circulatory disorders in the affected area (e.g. due to previous frostbite, diabetes, arteriosclerosis or ischemia),

-Patients with acute paroxysmal cold hemoglobinuria or cryoglobulinemia.

Figure 2 - Game Ready GR PRO 2.1 (https://gameready.com/gr-pro-cold-therapy-unit/)

The manufacturer of the device is the company CoolSystems®, Inc. (Concord, California 94520, USA). The GR PRO 2.1 device is provided for the study by MTR Health & Spa AG.

3.3 Preclinical Evidence

A limited number of studies have already shown that cooling in combination with compression has been able to achieve a positive influence compared to non-cooling measures. These positive effects could be presented on both a subjective and an objective level (Su et al. 2012; Leegwater et al. 2012; Waterman et al. 2012; Murgier and Cassard 2014; Klaber, Greeff, and O'Donnell 2019; Nabiyev et al. 2018; Bellon et al. 2019).

3.4 Clinical Evidence to Date

Current research results regarding the cooling and compression effects, on which this study is based, have been presented in chap. 3.3.

Ache

Waterman and colleagues found a significant difference in pain perception after 6 weeks in favor of cryotherapy in combination with compression, in patients with anterior cruciate ligament reconstruction (Waterman et al. 2012). Other studies also found less subjective pain postoperatively when cryotherapy with dynamic intermittent compression is used than static pain (Murgier and Cassard 2014; Klaber, Greeff, and O'Donnell 2019).

Questionnaires

With regard to different questionnaires (Lysholm; assesses different functions of the knee, SF-36; assesses daily activity or SANE; assesses the disease state), no significant differences could be found at any time (Waterman et al. 2012).

Range of motion

When the average knee flexion movement is measured, strongly significant results could be found in favor of cryopneumatic intervention (Murgier and Cassard 2014).

Medication

In a study with patients who received cryopneumatic intervention after a total knee prosthesis, it was shown that significantly fewer narcotic drugs were consumed 2 weeks postoperatively compared to the control group who received ice with static compression (Su et al. 2012). This is also confirmed by a study by Murgier and Cassard, which found statistically significant results in the average morphine application. Although there were no statistical differences in tramadol use, there was a clear trend in favor of dynamically intermittent cryocompression (Murgier and Cassard 2014). These results confirm another study that used pneumatic compression and cryotherapy after elective hip arthroplasty (Leegwater et al. 2012).

Functional outcomes

Functional outcomes such as the 6-minute walk test or the timed-up-and-go test were not significantly different in a study after 2 and 6 weeks, but showed a trend in the intervention group (Su et al. 2012).

Contentment

In the study by Su and her colleagues, subjective satisfaction was also assessed and showed significant results in contrast to the control intervention (Su et al. 2012).

Duration of stay

Two studies found that a combination with pneumatic compression and cryotherapy can lead to a shorter hospital stay compared to a normal compression bandage or standardized cryotherapy (Leegwater et al. 2012; Klaber, Greeff, and O'Donnell 2019).

These still discursive study results suggest that further research is needed to provide clear evidence-based recommendations regarding pneumatic compression in combination with cryotherapy. Currently, no research with the product GR PRO 2.1 or any other device from Game Ready (Concord, California, USA) is taking place in the research laboratory of the University of Applied Sciences and Arts Southern Switzerland, Physiotherapy Graubünden and the Regional Hospital Surselva AG, Spitalstrasse 6, CH-7130 Ilanz.

3.5 Justification for the design of the clinical investigation

In this study, the product Game Ready GR PRO 2.1 is used. This thermotherapy device is used as part of the intended application. The examiners apply cold including compression. The applied temperatures do not pose a danger to the test subjects at any time. The Game Ready GR PRO 2.1 generates temperatures from +5°C to +13°C. We will follow the following treatment program in this study: 48 hours after surgery, the intervention will start, if tolerable, with little compression (level 1 = 5-15 mmHg) and cooling at the coldest level tolerable by the participant (equivalent to program 2). The cooling should be perceived as "pleasant" by the participant. The intervention lasts one hour, of which 30 minutes are on and 30 minutes off cycles. The on cycle includes the duration of the intervention (cooling and compression), while the off cycles include the rest period. After 60 minutes, the device is removed. If compression is not tolerated, it can also be omitted (corresponds to program 1). The intervention is performed twice a day for the first four days after surgery. The coldest tolerable temperature level is determined anew with each treatment. The compression level can be increased depending on the participant. Medium compression may only be applied from the second day onwards (corresponds to programme 3). Doctors and physiotherapists can opt for cold treatments in their treatment. The question of whether the rehabilitation phase can be shortened or whether reintegration into everyday life can be increased by means of cooling applications including compression therapy is a legitimate question. These two parameters include not only objective values, but also subjective data.

3.6 Explanation for choice of comparator

Cooling/compression vs. control

Two groups are compared to each other in order to compare the effects of cooling including compression compared to the control group. For example, the efficiency of cooling including compression is to be examined for rehabilitation capability. The following treatment program is adhered to: 48 hours after the operation, the intervention starts, if tolerable, with little compression (level 1 = 5-15 mmHg) and cooling at the coldest level tolerable by the participant (corresponds to program 2). The cooling should be perceived as "pleasant" by the participant. The intervention lasts one hour, of which 30 minutes are on and 30 minutes off cycles. The on cycle includes the duration of the intervention (cooling and compression), while the off cycles include the rest period. After 60 minutes, the device is removed. If compression is not tolerated, it can also be omitted (corresponds to program 1). The intervention is performed twice a day for the first four days after surgery. The coldest tolerable temperature level is determined anew with each treatment. The compression level can be increased depending on the participant. Medium compression may only be applied from the second day onwards (corresponds to programme 3). The control group does not receive any cooling in addition to standard therapy.

Randomization

In order to produce a high-quality study, the subjects are each assigned to a group, which are later compared with each other.

The assignment is carried out randomly. Randomization is guaranteed by drawing a lot.

3.7 Risk evaluation (Risk-to-Benefits rationale)

There is minimal risk for the test subjects during cooling. The test subjects are expressly informed that they can stop the maximum tolerable cooling at any time. This also applies to integrated compression therapy. Furthermore, at least one examiner will be next to the subject during the cooling application in order to stop the intervention in the event of circulatory or other complaints. A fully equipped emergency kit is in the examination room at all times during the examinations. Since the intervention and measurements will take place on the premises of the Regionalspital Surselva AG, Spitalstrasse 6, CH-7130 Ilanz, first aid can be ordered directly in the event of circulatory and other problems. This information is communicated to the test persons (subject information). The device is used as recommended by the manufacturer.

3.8 Justification of the choice of the investigation population

Furthermore, any injuries and illnesses were defined as an exclusion criterion in order not to take the risk of intervention. The listed criteria are also recommended by the manufacturer.

More information on securing the test subjects can be found in chap. 8.1.1.

4. CLINICAL INVESTIGATION OBJECTIVES

4.1 Overall Objective

In this study, the effect of a maximum of 2x60 minutes of body section cooling including compression per day on the subjective assessment of everyday functions [score] as well as patient satisfaction [cm] and physiological inflammation parameters such as swelling [mm],
The pain scale [cm], skin temperature [°C], range of motion [degrees], morphine consumption [number] and length of stay [days] were examined. In addition, two assessments are used to assess everyday function: the 10-metre walk test [sec] and the timed-up-and-go [sec]. The effects of thermal application are compared to a control group and compared preoperatively, postoperatively (4th postoperative day) and after 6 weeks after surgery. The aim is to substantiate the state of scientific knowledge and to provide therapists and physicians with further insights. This study can benefit all those who work with patients after primary total knee arthroplasty.

4.2 Primary Objective

In this project, the effect of postoperative cooling on physiological parameters is measured and compared with the control group.

-Physical Function [Score]

-Patient satisfaction [cm]

-Joint circumference [mm]

-Range of motion [degrees]

-Skin temperature [°C]

-Morphine consumption [number]

-Visual analog scale [cm]

-Length of stay [days]

-10-meter walk test [sec]

-Timed-Up-and-Go [sec]

4.3 Secondary Objectives

-

4.4 Safety Objectives

No short-term risks are to be expected from this study other than those discussed so far.

5. CLINICAL INVESTIGATION OUTCOMES

5.1 Primary Outcome

This study aims to investigate the effects of cryotherapy with intermittent dynamic compression with Game Ready during a hospital stay. The preoperative measurement is the baseline, the 4th postoperative day is the primary endpoint and the measurement 6 weeks postoperative is declared as follow-up. The following parameters are examined for this purpose:

Questionnaire Physical Function [Score]

To determine the subjective assessment of physical function, the KOOS questionnaire is handed out, evaluated and documented. The KOOS questionnaire is highly valid for knee complaints and refers to the subjective impression of the patients (Roos and ToksvigLarsen 2003). The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

Patient satisfaction [cm]

In order to evaluate the patient satisfaction of the intervention group (Game Ready), the test subjects are asked the question "How satisfied are you with the cooling intervention?" immediately after the intervention. With the help of the Visual Analog Scale, the test subjects rate their satisfaction with a number between 0 (not at all satisfied) and 10 (maximally satisfied). The measurement moments take place twice a day (each time after the cooling intervention) during the

hospital stay.

Joint circumference [mm]

The joint circumference measurement is carried out by hand with a tape measure. This measurement method showed a high level of reliability. 5cm, 10cm, 15cm above the knee joint space, at the level of the knee joint space, 15cm below the knee joint space, above the lateral malleolus and above the scaphoid bone (Oesch 2007). Both sides are measured. The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

Range of motion [degrees]

To estimate the range of motion of knee flexion, the "RoMot" app from OT Bioelettronica (Turin, Italy) is used. The patient is in the supine position. The two sensors are applied to the lower and thigh legs. In response to the start command, the test subject tries to bend his knee as much as possible. The heel remains in bed and the longitudinal axis of the leg is also taken into account. Then the other side is measured. The number of degrees indicated by the software on the corresponding tablet is documented. Wireless Bluetooth sensors, for determining the amount of motion, show a high correlation compared to the goniometer measurements, which are currently the most commonly used in practice (Kumar et al. 2015). The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

Skin temperature [°C]

Skin temperature is also recorded with the help of an infrared thermometer (Voltcraft IR800-20D, Conrad Electronic, Hirschau, Germany). Handheld infrared thermal devices have high measurement accuracy (due to contact-free measurement) and practical handling (Stoop et al. 2020). Skin temperature is measured at four locations of the knee: superolateral, superomedia, inferiorlateral, and inferiordial margin of the patella (Zeng et al. 2016). The subject is in a supine position during the measurements. Both sides are measured. The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

Morphine consumption [number]

The number of morphine preparations taken per day is counted and documented.

Visual Analog Pain Scale [cm]

The Visual Analog Pain Scale is documented at rest (supine position). The scale is scaled from 0 (no pain) to 10 (greatest pain imaginable) in cm increments. The test subjects are asked the following question: "How severe is your knee pain?" The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

10-meter walk test [sec]

The 10-meter walking test is used because it is considered a valid and reliable measuring instrument for evaluating walking speed (Peters, Fritz, and Krotish 2013). In this assessment, the subject is asked to walk a distance of 10 meters as quickly and safely as possible. The examiner documents the time in seconds. The measurement moments take place preoperatively, on 4.
postoperative day and 6 weeks postoperatively.

Timed-Up-and-Go [sec]

The time-up-and-go is used because it is considered a valid and reliable measuring instrument for the evaluation of physical activity after hip and knee prostheses (Dobson et al. 2012). The subject is asked to rise from a chair while sitting and walk three meters, turn around and sit down again. The time spent on this task is measured in seconds. The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

Length of stay [days]

The number of hospitalisation days (from admission to and with discharge) is counted and documented.

5.2 Secondary outcomes

None available.

5.3 Other Outcomes of Interest

None available.

5.4 Safety Outcomes

No further outcomes are included that serve safety. Discontinuation of the experiment is the responsibility of the examiners with regard to the subject's resilience. If this is estimated to be too low, the examiner can stop the experiment. If the subject does not feel well according to his or her own subjective assessment, he or she can discontinue the experiment and withdraw participation in the study. If the cold application is not justifiable for the test subject, he or she can discontinue the application. There are no disadvantages for him/her as a result. The current regulations of the Canton of Graubünden and those of the FOPH for protection against the coronavirus will be taken into account and implemented when conducting the study.

6. CLINICAL INVESTIGATION DESIGN

6.1 General clinical investigation design and justification of design

Randomized, controlled trial

It is a clinical investigation concerning medical devices (MD), Category according to Art 6 ClinO-MD (A1), whereby a CE-certified medical device is tested in the intervention group.

The group size of the participants is n=28 people (per group n=14 people). The group assignment is randomized.

6.2 Methods for minimising bias

All measurements are carried out and logged by the same inspector in a standardized manner. The laboratory and hospital conditions are always the same.

6.2.1 Randomization

The allocation to the two different groups (Game Ready or Control group) takes place randomly when a ticket is drawn.

6.2.2 Blinding procedures

Blinding the participants is not possible in this study. The examiners are blinded by the addition of another examiner who operates the apparatus. The responsible statistician is blinded and has no access to the personal data of the test persons and is not present when the data is collected.

6.2.3 Other methods for minimising bias

The content of the conversation between the test persons and the examiner is kept to a minimum.

6.3 Unblinding Procedures (Code break)

There is no provision for the removal of the blinding of the statistician and the examiners.

The blinding of the examiners and the statistician is only permissible if an unforeseen incident would occur.

In the event of incidents (AEs) that occur during or shortly after study participation and may be attributable to the intervention, the principal investigator may, at his or her discretion, immediately waive the blinding of the study participant and the investigators present to ensure adequate treatment of the study participant.

In the case of incidents (AE) that occur longer than 24 hours, clarification by a doctor is mandatory and a doctor's certificate is required for the lifting of blindness. Data may then also be passed on to the attending physician with the consent of the study participant concerned. This approach is justified because no life-threatening incidents are to be expected due to the interventions used here.

7. CLINICAL INVESTIGATION POPULATION

7.1 Eligibility criteria

Subjects fulfilling all of the following inclusion criteria are eligible for the investigation:

- Signed Informed Consent by the participant

- Diagnosed gonarthrosis
- Planned implantation of a primary total knee endoprosthesis by the Regional Hospital Surselva AG

The presence of any one of the following exclusion criteria will lead to the exclusion of the subject:

- Decompensated hypertension in the affected area
- Acute inflammatory phlebitis in the affected area
- Patients with acute paroxysmal cold hemoglobinuria, or cryoglobulinemia
- significant vascular disorder in the affected area (e.g., due to previous frostbite, significant atherosclerosis, diabetes, or ischemic vascular disease)
- History of pulmonary embolism or risk factors for deep vein thrombosis or pulmonary embolism in the affected area
- Diseases such as active carcinomas or inflammation in the affected area, in which increased venous or lymphatic reflux is not desirable (as tumor cells and inflammatory parameters can be distributed throughout the body due to reflux)
- Severe or decompensated heart failure
- Raynaud's disease
- Hypersensitivity to cold
- Fear of cold/compression

The test subjects will be comprehensively informed about the process and possible risks before they are accepted to participate in the study. You will also receive the information in written form and have the opportunity to ask questions. The declaration of consent explains to them what their rights and obligations are when participating. In addition, they are informed that they may withdraw from participation at any time without giving reasons, without incurring any disadvantages as a result.

7.2 Recruitment and screening

Recruitment

It is advertised in the consultation hours of the orthopaedists of the Regionalspital Surselva AG, Spitalstrasse 6, CH7130 Ilanz with the help of the created advertisement (see attachment). The exact texts have been prepared according to the checklist of the Cantonal Ethics Commission Zurich.

Screening

At the first contact, the potential participants are informed about the course and risks of the study, as well as its conditions and the amount of compensation.

Advertisement

The advertisement for the first contact can be found in the attachment.

7.3 Assignment to investigation groups

The group assignment is hidden with the help of a ticket in a sealed envelope, which is drawn under the supervision of the study director. This lot shows whether the subject is going through the Game Ready or Control intervention.

7.4 Criteria for withdrawal / discontinuation of subjects

If a participant withdraws from the study, the allocation lot is returned to the pot in a new envelope and a new participant is sought.

The already completed consent form is kept in the locked filing cabinet. In the event of a revocation of consent, the data and samples already collected must be included in the evaluation for scientific and security reasons. Only after the analysis are they anonymised (Art. 9 ClinO).

The conditions for the termination of the experiment were described in chap. 5.4.

There is no disadvantage for the participants in the event of a termination of the Study participation.

8. CLINICAL INVESTIGATION INTERVENTION

8.1 Identity of the medical device under investigation

8.1.1 Experimental Intervention (medical device)

The Game Ready GR PRO 2.1 builds on the groundbreaking Game Ready technology and is a multimodality recovery device for professional users. The system can deliver ice-free cold treatment and intermittent pneumatic compression treatment, providing healthcare professionals with flexible options for different patients, procedures, injuries and rehabilitation stages.

Proven principles such as PITCH (pause, ice, compression, elevation) can be taken to a new level with the state-of-the-art Game Ready GR PRO 2.1. Cumbersome procedures for cold treatment will be simplified with the compact, practical device. In addition, these can be monitored and controlled more consistently than conventional methods. The device is controlled via a touchscreen computer interface. The user can choose between different treatment modalities and easily change and monitor the settings for treatment duration, temperature and compression. The double-acting (cryotherapy and compression) and anatomically designed Game Ready cuffs can be used specifically for specific parts of the body.

This device is used for the treatment of post-traumatic, post-operative (medical and/or surgical) and acute injuries, as well as for the reduction of edema, swelling and pain when cold and compression are indicated. It works in a closed circle with the help of the cuff described above and is therefore hygienic and safe to use in the clinic. The device is already being used in several Swiss clinics and institutions.

Figure 3 - Game Ready GR PRO 2.1 (https://gameready.com/gr-pro-cold-therapy-unit/)

In addition to standard physiotherapy (see Chapter 8.1.2 for more information), the subjects in the intervention group will receive the following intervention (according to the manufacturer's protocol for patients with total knee endoprosthesis): 48 hours after the operation, the intervention starts, if tolerable, with little compression (level 1 = 5-15 mmHg) and cooling at the coldest level tolerable by the participant (corresponds to program 2). The cooling should be perceived as "pleasant" by the participant. The intervention lasts one hour, of which 30 minutes are on and 30 minutes off cycles. The on cycle includes the duration of the intervention (cooling and compression), while the off cycles include the rest period. After 60 minutes, the device is removed. If compression is not tolerated, it can also be omitted on the first postoperative day (corresponds to program 1). The intervention is performed twice a day for the first four days after surgery. The coldest tolerable temperature level is to be determined anew for each treatment. The compression level may be increased, although medium compression may only be applied from the second day onwards (corresponds to program 3).

Securing study participants

The Game Ready applications represent a commonly used cooling and compression intervention in the literature. Nevertheless, the test subjects can discontinue the treatment at any time if they feel unwell. During the cooling applications and measurements, at least one or two examiners will always be next to the test subject in order to discontinue the treatment in case of discomfort. Further precautions are described in chap. 3.7. Risk/Benefits Described.

8.1.2 Control Intervention (standard/routine/comparator)

The test subjects receive standard physiotherapy, without Game Ready application. Standard physiotherapy after a total knee prosthesis includes the following interventions: The first physiotherapeutic treatment begins on the first postoperative day and consists of immediate loading of the operated leg (full weight bearing permitted according to the symptoms). Knee mobilisation with a passive movement machine and active knee mobilisation, instructed by the physiotherapist, are carried out. The treatment is carried out and documented by qualified and training physiotherapists at the Regional Hospital Surselva AG, Spitalstrasse 6, CH-7130 Ilanz. The cooling applications with Game Ready do not conflict with standard therapy.

8.1.3 Labelling and Supply (re-supply)

The Game Ready GR PRO 2.1 is a certified medical device that complies with European regulations, directives and standards (93/42/EEC, EN60601-1, EC 60601-1-2, CE 0086).

8.1.4 Storage Conditions

The Game Ready must be stored inside a room. The appliance is therefore located all year round in a closed room at room temperature and low humidity.

8.2 Discontinuation or modifications of the intervention

No further side effects are expected from participation in the study, as it is not an invasive method or drug intervention. As in chap. 8.5, the predefined inclusion and exclusion criteria as well as the health questionnaire are used to ensure safe participation. However, if reasons arise, the study participant reserves the right to withdraw from the study early. The test person reserves the right to exclude a participant from the study for the following reasons: safety aspects (feeling unwell, dissatisfaction of the participant), occurrence of one of the predefined exclusion criteria, at the request of the participant, revocation of consent (also possible without justification). Further information in this case can be found under chap. 9.2.5 and 7.4.

8.3 Compliance with clinical investigation intervention

Due to the fact that at least one research employee will be present during the Game Ready applications and the measurements, the compliance of the study participants can be classified as high. No additional measures are taken to improve compliance.

8.4 Data Collection and Follow-up for withdrawn subjects

The medical follow-up of subjects who drop out of the examination prematurely is described in chapters 9.2.5 and 9.2.6. There is no disadvantage for the participants if they discontinue their participation in the study and no further interventions are necessary for follow-up treatment.

8.5 Clinical investigation specific preventive measures

Furthermore, any injuries and illnesses were defined as an exclusion criterion in order not to take the risk of intervention. The questionnaire also asks about any diseases and influences that preclude participation in the study. If there are doubts that are not medically proven, the study leader reserves the right to have them checked and thus exclude a test subject from participation.

8.6 Concomitant Interventions (treatments)

No interventions will be carried out in the study other than those described in Chapter 8.1. Therefore, no further side effects are expected from participation in the study.

8.7 Medical Device Accountability

The trials are taking place exclusively at the Regional Hospital Surselva AG, Spitalstrasse 6, CH-7130 Ilanz. This means that there is no transport of the products and measuring instruments used. There is therefore no liability for the transport of the product.

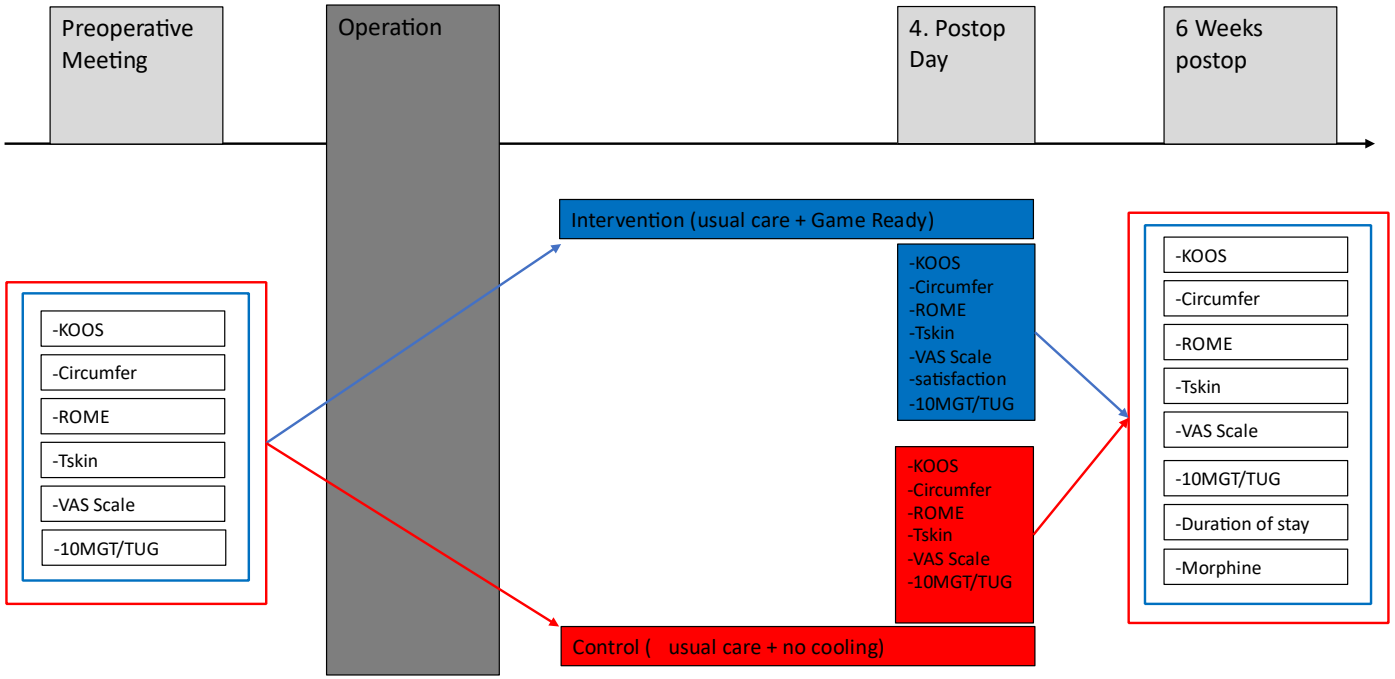
8.8 Return, Analysis or Destruction of the Medical Device

The Game Ready GR PRO 2.1 will be returned to MTR at the end of the measurement period. In the event of product defects, including malfunctions, usability issues, or insufficient information from the manufacturer, including labeling, the products will be returned to the sponsor for analysis.

SUPSI

9. CLINICAL INVESTIGATION ASSESSMENTS

Procedure Game Ready - Study



SUPSI

9.1 Clinical investigation flow chart(s) / table of clinical investigation procedures and assessments

The test subject information is sent to the test subjects' homes in advance or given in person during the orthopaedic consultation. All rounds take place on the premises of the Regional Hospital Surselva AG.

1. ***Subject Information & Informed Consent Meeting***

   30 min (questions and ambiguities will be discussed individually here)

2. ***Running the Test Log***

Test log	
Cooling group	Control group
Visit 1: Screening and baseline preoperatively: information, written consent, examination of /Exclusion criteria, health questionnaire Physical Function [Score] Joint circumference [mm] Range of motion [degrees] Skin temperature [°C] Visual Analog Pain Scale [cm] 10-meter walk test [sec] Timed-up-and-Go [sec]	**Visit 1:** Preoperative screening and baseline information, written consent, examination of /Exclusion criteria, health questionnaire Physical Function [Score] Joint circumference [mm] Range of motion [degrees] Skin temperature [°C] Visual Analog Pain Scale [cm] 10-meter walk test [sec] Timed-up-and-Go [sec]
Daily cooling intervention In addition to the usual physiotherapeutic treatment: Daily Cooling and compression. One detailed treatment description can be found in chap. 8.1.1.	**Daily Control Intervention** In addition to the usual physiotherapeutic Treatment: No refrigeration (see chapter 8)
Visit 4: Follow up 4th postoperative day Physical Function [Score] Joint circumference [mm] Range of motion [degrees] Skin temperature [°C] Visual Analog Pain Scale [cm] Patient satisfaction [cm] 10-meter walk test [sec] Timed-up-and-Go [sec]	**Visit 4:** Follow up 4th postoperative day Physical Function [Score] Joint circumference [mm] Range of motion [degrees] Skin temperature [°C] Visual Analog Pain Scale [cm] 10-meter walk test [sec] Timed-up-and-Go [sec]

Visit 5: Follow up 6 weeks postoperatively Physical function [Score] Joint circumference [mm] Range of motion [degrees] Skin temperature [°C] Visual Analog Pain Scale [cm]	**Visit 5:** Follow up 6 weeks postoperatively Physical function [Score] Joint circumference [mm] Range of motion [degrees] Skin temperature [°C] Visual Analog Pain Scale [cm]
10-meter walk test [sec] Timed-up-and-Go [sec] Length of stay [days] Morphine consumption [number]	10-meter walk test [sec] Timed-up-and-Go [sec] Length of stay [days] Morphine consumption [number]

Test log	
Rounds	Time exposure
Visit 1: Screening and baseline preoperatively: information, written consent, examination of /Exclusion criteria, health questionnaire Physical Function [Score] Joint circumference [mm] Range of motion [degrees] Skin temperature [°C] Visual Analog Pain Scale [cm] 10-meter walk test [sec] Timed-up-and-Go [sec]	60 min
Daily cooling intervention In addition to the usual physiotherapeutic treatment: Daily Cooling and compression. One detailed treatment description can be found in chap. 8.1.1.	2x daily one treatment of 60 min = 120 min per day 4x 120 min per day = 480 min per stay
Visit 2: Follow up 4th postoperative day Physical Function [Score] Joint circumference [mm] Range of motion [degrees] Skin temperature [°C] Visual Analog Pain Scale [cm] Patient satisfaction [cm] 10-meter walk test [sec] Timed-up-and-Go [sec]	30 min

Visit 3: Follow up 6 weeks postoperatively Physical Function [Score] Joint circumference [mm] Range of motion [degrees] Skin temperature [°C] Visual Analog Pain Scale [cm] 10-meter walk test [sec] Timed-up-and-Go [sec] Length of stay [days] Morphine consumption [number]	40 min
Total time commitment:	610 min

Any adverse events must be recorded during each visit. These possible time expenditures are not included in the test protocol.

9.2 Assessments of outcomes

The following data are collected during all tests described in the sub-protocols in chap. 9.1.

9.2.1 Assessment of primary outcome

Questionnaire Physical Function [Score]

To determine the subjective assessment of physical function, the KOOS questionnaire is handed out, evaluated and documented. The KOOS questionnaire is highly valid for knee complaints and refers to the subjective impression of the patients (Roos and ToksvigLarsen 2003). The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

Patient satisfaction [cm]

In order to evaluate the patient satisfaction of the intervention group (Game Ready), the test subjects are asked the question "How satisfied are you with the cooling intervention?" immediately after the intervention. With the help of the Visual Analog Scale, the test subjects rate their satisfaction with a number between 0 (not at all satisfied) and 10 (maximally satisfied). The measurement moments take place twice a day (each time after the cooling intervention) during the
hospital stay.

Joint circumference [mm]

The joint circumference measurement is carried out by hand with a tape measure. This measurement method showed a high level of reliability. 5cm, 10cm, 15cm above the knee joint space, at the level of the knee joint space, 15cm below the knee joint space, above the lateral malleolus and above the scaphoid bone (Oesch 2007). Both sides are measured. The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

Range of motion [degrees]

To estimate the range of motion of knee flexion, the "RoMot" app from OT Bioelettronica (Turin, Italy) is used. The patient is in the supine position. The two sensors are applied to the lower and thigh legs. In response to the start command, the test subject tries to bend his knee as much as possible. The heel remains in bed and the longitudinal axis of the leg is also taken into account. Then the other side is measured. The number of degrees indicated by the software on the corresponding tablet is documented. Wireless Bluetooth sensors, for determining the amount of motion, show a high correlation compared to the goniometer measurements, which are currently the most commonly used in practice (Kumar et al. 2015). The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

Skin temperature [°C]

Skin temperature is also recorded with the help of an infrared thermometer (Voltcraft IR800-20D, Conrad Electronic, Hirschau, Germany). Handheld infrared thermal devices have high measurement accuracy (due to contact-free measurement) and practical handling (Stoop et al. 2020). Skin temperature is measured at four locations of the knee: superolateral, superomedia, inferiorlateral, and inferiordial

margin of the patella (Zeng et al. 2016). The subject is in a supine position during the measurements. Both sides are measured. The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

Morphine consumption [number]

The number of morphine preparations taken per day is counted and documented.

Visual Analog Pain Scale [cm]

The Visual Analog Pain Scale is documented at rest. The scale is scaled from 0 (no pain) to 10 (greatest pain imaginable) in cm increments. The test subjects are asked the following question: "How severe is your knee pain?" The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

10-meter walk test [sec]

The 10-meter walking test is used because it is considered a valid and reliable measuring instrument for evaluating walking speed (Peters, Fritz, and Krotish 2013). In this assessment, the subject is asked to walk a distance of 10 meters as quickly and safely as possible. The examiner documents the time in seconds. The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

Timed-Up-and-Go [sec]

The time-up-and-go is used because it is considered a valid and reliable measuring instrument for the evaluation of physical activity after hip and knee prostheses (Dobson et al. 2012). The subject is asked to rise from a chair while sitting and walk three meters, turn around and sit down again. The time spent on this task is measured in seconds. The measurement moments take place preoperatively, on the 4th postoperative day and 6 weeks postoperatively.

Length of stay [days]

The number of hospitalisation days (from admission to and with discharge) is counted and documented.

9.2.2 Assessment of secondary outcomes

None available.

9.2.3 Assessment of other outcomes of interest

None available.

9.2.4 Assessment of safety outcomes

No corresponding parameters are collected.

9.2.4.1 Adverse events

-

9.2.4.2 Laboratory parameters

-

9.2.4.3 Vital signs

-

9.2.5 Assessments in subjects who prematurely stop the clinical investigation

For the participants, there is no disadvantage in the event of an (arbitrary) discontinuation of study participation and no further interventions are necessary for follow-up treatment.

However, if study participation was discontinued due to an injury sustained during study participation, this will be recorded and reported to the sponsor, the head of the research laboratory, the study leader and the supervisor of the study. The report is then sent to the business liability insurance of Thim van der Laan AG in order to ensure the appropriate follow-up treatment.

The following are recorded:

- Date and time of the incident
- Course of the incident

- Persons involved & witnesses
- Study ID (issued by the CEC)
- Personal details of the person concerned (if not previously recorded)

9.2.6 Follow-up of the subjects after the regular termination of the clinical investigation

Since the Game Ready GR PRO 2.1 thermotherapy device used is only used in the context of the intended use, no additional care of the subject is required after the end of his or her participation in the clinical trial, nor are arrangements made for subsequent care.

9.3 Procedures at each visit

All rounds take place on the premises of the Regional Hospital Surselva AG.

9.3.1 Single measurement

The project consists of multiple visits with a total duration of 850 minutes, which takes place as follows:

9.3.2 Multiple visits

Responsibility for conducting the study and protecting participants Responsibility: Dr.

Ron Clijsen

1. Subject Information & Informed Consent

The "Visit 1: Screening" includes the following steps: The test subjects are subjected to a screening before being accepted
participation in the study is comprehensively informed about the process and possible risks. You will also receive the information in written form and have the opportunity to ask questions. The declaration of consent explains to you what your rights and obligations are when participating and that you may withdraw from participation at any time without giving reasons, without any disadvantage to you. More detailed information can be found in chap. 2.7. Responsibility: Dr. med. Martin Wonerow, Dr. med. Sebastian Ulsamer

2. Running the Test Log

Visit 1: Screening describes the collection of baseline values (preoperatively) as well as any further information, written consent, examination of all inclusion/exclusion criteria, and the health questionnaire.

Start of the cooling intervention: In addition to the usual physiotherapeutic treatment: Daily
Cooling and compression. A detailed description of the intervention can be found in chap. 8.1.1.

Visit 2 and 3: The measurements are carried out in the same way as the test protocol and the data is collected.

Responsibility: Research staff of the University of Applied Sciences and Arts Southern Switzerland

3. Indemnification and Conclusion

After completion of the measurements (6 weeks postoperatively), the subject will receive the compensation due according to the information in the advertisement: a flat rate of CHF 50 after completion of the measurements.

Responsibility: Research staff of the University of Applied Sciences and Arts Southern Switzerland

10. SAFETY

10.1 Definition and Assessment of (Serious) Adverse Events and other safety related events

Adverse Event (AE) (Art. 2 para. 57 MDR)

Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the MD.

Serious Adverse Event (SAE) (Art. 2 para. 58 MDR) Any adverse event that led to any of the following:

(a) Death
(b) serious deterioration in the health of the subject that resulted in any of the following:
  (i) life-threatening illness or injury,
  (ii) permanent impairment of a body structure or a body function,
  (iii) hospitalisation or prolongation of patient hospitalisation,
  (iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
  (v) chronic disease,
(c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Note: planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration of the health status of the subject, is not considered an SAE

Device deficiency (Art. 2 para. 59 MDR)

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, of an investigational device, including malfunction, user errors and inadequate information supplied by the manufacturer.

Malfunction (ISO14155)

Failure of an investigational device to perform in accordance with its intended purpose when used in accordance with the instructions for use or the CIP.

Device deficiency with Serious Adverse Device Effect (SADE) potential (Art. 80 para. 1 letter c MDR; ISO14155)

Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Adverse Device Effect (ADE) (ISO14155)

Adverse event possibly, probably or causally related to the use of an investigational device or procedures.

Serious Adverse Device Effect (SADE) (ISO14155)

Adverse device effect (ADE) that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE) (ISO14155)

Serious adverse device effect (SADE) which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Causal Relationship of SAE (MDCG 2020-10/1)

A causal relationship towards the medical device or the procedure of the investigation should be rated by the PI and the Sponsor as follows:

- **Not related:** The relationship to the device or procedures can be excluded.
- **Possible:** The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible.
- **Probable:** The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause.

- **Causal relationship:** The serious event is associated with the investigational device or with procedures beyond reasonable doubt.

10.2 Adverse events categorization

The adverse events are categorized by the PI and the Sponsor using the following algorithm: Does the AE meet the seriousness criteria?

- No, it is not serious
  - Is the relationship to the device or the procedure possible, probable or causal?
  - No: non-related AE
  - Yes: ADE
- Yes, it is serious: SAE
  - Is the relationship to the device or the procedure possible, probable or causal?
  - No: non-related SAE
  - Yes: SADE
- Is it anticipated (within expected type, severity and frequency of the complications)?
  - No: unanticipated SADE (USADE)
  - Yes: anticipated SADE (ASADE)

10.3 Documentation and reporting in Medical Device Category A clinical investigations

Device deficiencies (DD) and all **adverse events (AE)** including all **serious adverse events (SAE)** are collected, fully investigated and documented in the source document and appropriate case report form (CRF) during the entire investigation period, i.e. from patient's informed consent until the last CIPspecific procedure, including a safety follow-up period.

- Documentation of AEs (including SAEs) by the PI includes diagnosis or symptoms, start and stop dates of event, event treatment, event resolution, assessment of seriousness and causal relationship to MD and/or investigation procedure (Art. 32 ClinO-MD, ISO14155).
- Documentation of DDs by the PI includes description of event, start date, investigational device information, action taken with regard to the investigational device, and whether the DD led to an AE. The Sponsor shall review all DDs and determine and document in writing whether they could have led to a SAE (DD with SADE potential) (Art 32. ClinO-MD, ISO14155).

The project works with a CE-certified product. It is a study with 30 or fewer subjects. The study focuses on basic findings. The study aims to gain fundamental knowledge in the field of cryotherapy in combination with compression. The monitoring for quality assurance is carried out by Prof. Peter Clarys, PhD.

10.3.1 Foreseeable adverse events and anticipated adverse device effects

The following foreseeable serious adverse events and product defects may occur:

-tissue damage due to improper or too long use than described by the manufacturer,

-burning, itching, increasing swelling, pain, blisters, increasing redness, discoloration and other visible changes during treatment,

-Change in wound conditions (if the wrap is not applied over the bandage or clothing),

-Risk of electric shock (if other power supplies are used, housing parts are removed, or damaged cables and connecting hoses are used) and

-Device damage (if there is no or too hot water in the ice box, the device is lifted up by the lid, or wraps from other manufacturers have been used).

Participants who complain of ongoing adverse events after graduation/discontinuation of their studies will be contacted by telephone two weeks after graduation and asked about their state of health. If the

undesirable events still exist, the participants will be called up for an additional visit to the Surselva Regional Hospital AG. During this visit, the ongoing events are assessed and documented.

10.3.2 Reporting of Safety related events

Reporting to the Sponsor:

All SAEs, device deficiencies and health hazards that require measures are reported to the Sponsor by the PI (or authorized designee) within 24 hours after becoming aware of the event. Device deficiencies are assessed regarding their potential to lead to an SAE. DD are assessed regarding their potential to lead to an SAE.

Reporting to the Competent Ethics Committee:

The Sponsor reports to the CEC promptly any serious adverse event which has a causal relation with the MD, comparator or procedure/test method or where a causal relation appears to be possible (Art. 33 ClinO-MD).

In order to ensure prompt notification, the Sponsor may initially submit an incomplete notification.

If safety and health hazards that require measures must be taken immediately during the conduct of the investigation, the Sponsor notifies the CEC within 2 days of these measures and the circumstances which made them necessary (Art. 34 ClinO-MD).

Periodic safety reporting (Art. 35 ClinO-MD):

An Annual Safety Report (ASR) is submitted by the Sponsor to the CEC, yearly. The ASR contains a list of all SADEs and DDs and a report on their degree of seriousness, causal relationship with the MD and procedure and on subjects' safety.

Other reporting is done according to provisions of MD vigilance as per Art. 87-90 MDR (Art. 33 para. 4.b ClinO-MD) and Art. 67 MedDO.

11. STATISTICAL METHODS

11.1 Hypothesis

Physical Function [AU]

H0: The use of cryotherapy with intermittent dynamic compression has no positive effect on the physical functions of patients after a total knee arthroplasty.

H1: The use of cryotherapy with intermittent dynamic compression has a positive effect on the physical functions of patients after a total knee arthroplasty.

Patient satisfaction [cm]

H0: The use of cryotherapy with intermittent dynamic compression has no positive effect on patient satisfaction of patients after a total knee arthroplasty.

H1: The use of cryotherapy with intermittent dynamic compression has a positive effect on patient satisfaction of patients after a total knee arthroplasty.

Joint circumference [mm]

H0: The joint circumference is not reduced by cryotherapy with intermittent dynamic compression compared to the control group during a hospital stay.

H1: The joint circumference is reduced by cryotherapy with intermittent dynamic compression compared to the control group during a hospital stay.

Skin temperature [C°]

H0: The skin temperature is not reduced by cryotherapy with intermittent dynamic compression compared to the control group during a hospital stay.

H1: The skin temperature is reduced by cryotherapy with intermittent dynamic compression compared to the control group during a hospital stay.

Morphine consumption [number]

H0: The intake of morphine is not reduced by cryotherapy with intermittent dynamic compression compared to control groups during hospitalization.

H1: The intake of morphine is reduced by cryotherapy with intermittent dynamic compression compared to the control group during a hospital stay.

Visual analog scale [cm]

H0: The sensation of pain with the Visual Analog scale is not reduced by cryotherapy with intermittent dynamic compression compared to the control group during a hospital stay.

H1: The sensation of pain with the Visual analog scale is reduced by cryotherapy with intermittent dynamic compression compared to the control group during a hospital stay.

10-meter walk test [sec]

H0: The 10-metre gait test is not reduced by cryotherapy with intermittent dynamic compression compared to control groups during a hospital stay.

H1: The 10-metre gait test is reduced by cryotherapy with intermittent dynamic compression compared to the control group during a hospital stay.

Timed-Up-and-Go [sec]

H0: The timed up-and-go is not reduced by cryotherapy with intermittent dynamic compression compared to control groups during a hospital stay.

H1: The timed-up-and-go is reduced by cryotherapy with intermittent dynamic compression compared to control groups during a hospital stay.

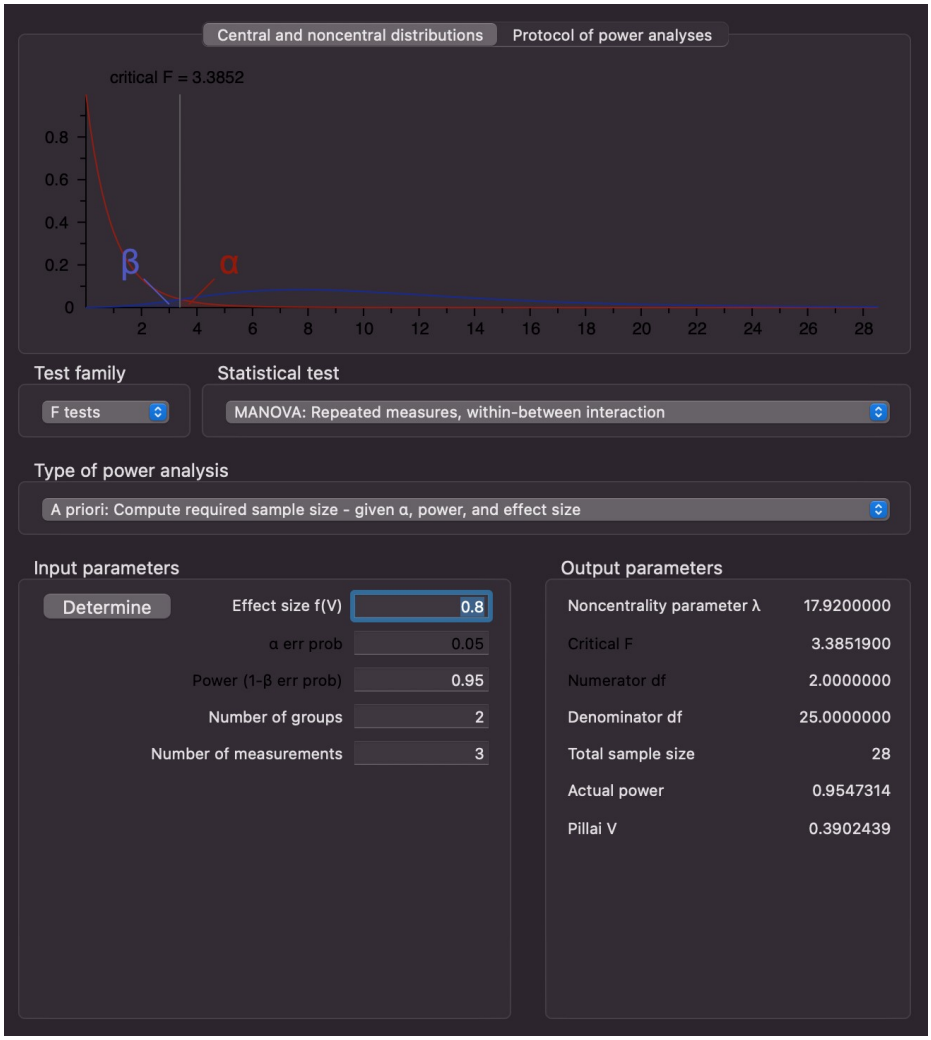
Length of stay [days]

H0: The length of stay in hospital is not shortened by cryotherapy with intermittent dynamic compression compared to control groups during a hospital stay. H1: The length of stay in hospital is shortened by cryotherapy with intermittent dynamic compression compared to control groups during a hospital stay.

11.2 Determination of Sample Size

A power analysis was performed using the G*Power App (Düsseldorf, North Rhine-Westphalia, DEU), where a minimum number of 28 subjects was deemed necessary to ensure the statistical power (0.95) to detect a parameter difference at the 5% significance level. The figure below shows the G-Power calculation that was used to determine the sample size.

Figure 4: Sample Size Calculation



11.3 Statistical criteria of termination of the investigation

Only data from subjects who have completed the entire protocol will be included in the study. This ensures that all data has been collected under the same conditions and thus remains homogeneous and comparable.

11.4 Planned Analyses

11.4.1 Datasets to be analysed, analysis populations

Only complete data sets will be included in the study. Data that contains only part of the protocol is not included in the analysis. No new subjects are being sought to replace the missing data.

11.4.2 Primary Analysis

The statistical data analysis will be carried out by Dr. Erich Hohenauer after completion of the data collection of the entire project.

Repeated measures analysis of variance (MANOVA) 2

factors:

Factor 1: Intervention (Game Ready vs. Control Intervention)

Factor 2: Time (baseline, 4th postoperative day and 6 weeks)

The significance level is set to $p<0.05$. Statistical data analysis is carried out with SPSS.

11.4.3 Secondary Analyses

Repeated measures analysis of variance (MANOVA) 2

factors:

Factor 1: Intervention (intervention side vs. control side)

Factor 2: Time (baseline, 4th postoperative day and 6 weeks)

The significance level is set to $p<0.05$. Statistical data analysis is carried out with SPSS.

11.4.4 Interim analyses

The data is processed after the end of the respective subprotocol. Thus, the data analysis for the entire study takes place in stages. No additional interim analyses are planned.

11.4.5 Deviation(s) from the original statistical plan

Deviations from the planned statistical analysis are recorded and justified and reported to the CEC in the annual report.

11.5 Handling of missing data and drop-outs

If a test subject does not complete the experiment, any data that has already been collected is retained, but is not further incorporated into the final data analysis.

12. QUALITY ASSURANCE AND CONTROL

12.1 Data handling and record keeping / archiving

12.1.1 Case Report Forms

Data protection and confidentiality are guaranteed and no personal data is presented or published. The signed declaration of consent, as well as the completed questionnaire with the other personal data and demographic and medical personal data are stored in the original as a study document in a locked filing cabinet. The identity of the test persons is encoded in accordance with the encryption (coding) of a person when participating in a research project, as accepted by swissethics. Only a person's year of birth (YYYY) is documented along with a coding number in the CRF. The project manager is responsible for the secure storage of the key for the data encrypted as part of the clinical trial or research project. Direct access to the personal data will continue to be allowed only to authorized persons of the CEC.

12.1.2 Specification of source data and source documents

The data collected in writing are recorded on paper in the enclosures and are marked as study data. In a double-blind process, the data is transferred from the CRF to an Excel database for the analyses. They are therefore subject to data protection and are regulated in accordance with the provisions set out in chap. 12.1.1.

12.1.3 Archiving of essential clinical investigation documents

All the documents of the investigation must be archived for a minimum of 10 years after regular or premature termination of the investigation. Data protection will continue to be guaranteed.

12.2 Data management

12.2.1 Data Management System

The questionnaire for recording physical function is obtained by hand. All other outcomes (joint circumference, range of motion, morphine consumption, VAS scale, length of stay, 10-metre walk test, timed-up-and-go) are noted on the data collection form. Excel is used for further data analysis. Windows Excel will also be used for data pooling and for the graphical representation of® the end data. All data is processed on the central research computer. This research computer is located at all times in Landquart (research laboratory). Only the study director and the examiners know the password to unlock this computer. All digital documents are read-only by a password. Only the study director and the examiners know the passwords of the digital documents. The digital documents will be given version numbers. Changes made to the digital documents are saved as a new version number. In addition, all versions will be printed out and signed by the Director of Studies. The printed documents are stored in a separate, lockable filing cabinet. This filing cabinet also contains the password combinations to decrypt the computer and edit the documents. Only the director of studies has the key to this filing cabinet.

12.2.2 Data security, access and back-up

The data is encrypted and treated confidentially, access to the personal data is not allowed to third parties. The digital data collected is stored solely on the institute's own computers and is not passed on to any external persons or to other parties.
Transfer computer. Access to the computers of the research laboratory at the "University of Applied Sciences and Arts Southern Switzerland" is only granted to the head of studies and the examiners as well as persons authorised by the CEC.

12.2.3 Analysis and archiving

After collection, the data is encrypted and stored on another external hard drive for further backup. This is stored in a locked filing cabinet to ensure data protection.

12.2.4 Electronic and central data validation

Immediately after data collection, the quality of the data is checked and verified with the help of the visual representation.

12.3 Monitoring

The collected data can be viewed by authorized persons at any time. Remote monitoring of the study is planned by the following person:

Prof. Peter Clarys, PhD

Vrije Universiteit Brussels

Faculty of Physical Therapy Pleinlaan

2, 1050 Brussels

peter.clarys@vub.ac.be

Monitoring is regulated in a separate agreement. The monitoring of the study will be carried out externally and virtually (without physical presence). The documents to be checked are made available to the monitor for inspection on a protected page of the Microsoft Teams platform.

12.4 Audits and Inspections

A report on the current status of the study is sent monthly to the study supervisor (Prof. Dr.
Peter Clarys). This also includes demonstrating and presenting results and statistical analyses. An annual report on the course of the study will be submitted to the CEC. Authorized persons of the CEC can view the data forms as well as the digital data on the institute's own computers at any time. Data protection is guaranteed at all times.

12.5 Confidentiality, Data Protection

The examiners ensure that the privacy of the participants is maintained. In particular, data protection and confidentiality are guaranteed and no personal data is presented or published. The signed declaration of consent, as well as the completed questionnaire with the other personal details, are kept in the original as a study document in a locked filing cabinet. The data is encrypted and treated confidentially, access to the personal data is not allowed to third parties. The digital data collected is stored solely on the institute's own computers and is not passed on to any external persons or transferred to other computers. Direct access to the personal data is only allowed to authorized persons of the CEC.

13. PUBLICATION AND DISSEMINATION POLICY

The examiners ensure that the privacy of the participants is maintained. In particular, the data protection and confidentiality of the data are guaranteed and no personal data is presented or published nor passed on to outsiders and unauthorized persons.

14. FUNDING AND SUPPORT

14.1 Funding

The study is funded by the University of Applied Sciences and Arts Southern Switzerland, Physiotherapy Graubünden. The auditors are employed by this institute and are remunerated for their work on this study in accordance with their employment contracts. No further financial support is needed.

14.2 Other Support

The Game Ready GRPro 2.1 thermotherapy device is kindly provided by the Swiss distributor MTR Health & Spa AG for the entire duration of the study. There is no written agreement. However, no obligations have been entered into towards the company and the independence of data analysis and discussion is thus guaranteed. **MTR Health & Spa AG**

Fällmisstrasse 64

CH-8832 Wilen b. Wollerau

Phone: +41 (0)44 787 70 80

Fax: +41 (0)44 787 70 81

15. INSURANCE

There is a business liability insurance with Baloise Insurance for Thim van der Laan AG in Landquart. Any damage in connection with the research activities at the Regionalspital Surselva AG is covered by the public liability insurance of the Regionalspital Surselva AG. A confirmation is attached to this application.

16. REFERENCES

1. Declaration of Helsinki, Version October 2013 (http://www.wma.net/en/30publications/10policies/b3/index.html)
2. Human Research Act, HFG Federal Act on Human Research (Federal Act on Human Research, HFA) of 30 September 2011/ Loi fédérale relative à la recherche sur l'être humain (loi relative à la recherche sur l'être humain, LRH) du 30 septembre 2011 / Legge federale concernente la ricerca sull'essere umano (Legge sulla ricerca umana, LRUm) del 30 settembre 2011
3. Ordinance on Clinical Trials on Medical Devices (ClinV-Mep) of 1 July 2020 / Ordonnance sur les essais cliniques de dispositifs médicaux (OClin-Dim) du 1er juillet 2020 /. Ordinanza sulle sperimentazioni cliniche con dispositivi medici (OSRUm-Dmed) del 1 luglio 2020
4. Ordinance on Clinical Trials in Human Research (Ordinance on Clinical Trials, KlinV) of 20 September 2013 / Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain (Ordonnance sur les essais cliniques, OClin) du 20 septembre 2013. (Ordinanza sulle sperimentazioni cliniche, OSRUm) del 20 settembre 2013
5. Medical Devices Regulation (MedDO) of 17 October 2001 / Ordonnance sur les dispositifs médicaux (ODim) du 17 octobre 2001 / Ordinanza relativa ai dispositivi medici (ODmed) del 17 ottobre 2001
6. Medical Device Regulation (EU) 2017/745 of 5 April 2017 (MDR) (https://eurlex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32017R0745)
7. MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 (https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-101_guidance_safety_reporting_en.pdf)
8. EN ISO 14155: Clinical investigation of medical devices for human subjects - Good clinical practice (www.iso.org)
9. EN ISO 10993: Biological evaluation of medical devices (www.iso.org)
10. EN ISO 14971: Application of risk management to medical devices (www.iso.org)
11. WHO, International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
12. Radiation Protection Ordinance (StSV) of 26 April 2017 / Ordonnance sur la radioprotection (ORaP) du 26 avril 2017 / Ordinanza sulla radioprotezione (ORaP) del 26 aprile 2017.
13. International Conference on Harmonization (ICH) Guideline for Good Clinical Practice E6(R2). (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4.pdf)

Bellon, M., D. Michelet, N. Carrara, T. Vacher, B. Gafsou, B. Ilhareborde, K. Mazda, E. Ferrero, A. L. Simon, F. Julien-Marsollier, and S. Dahmani. 2019. "Efficacy of the Game Ready((R)) cooling device on postoperative analgesia after scoliosis surgery in children." *Eur Spine J* 28 (6): 1257-1264. https://doi.org/10.1007/s00586-019-05886-6. https://www.ncbi.nlm.nih.gov/pubmed/30847706.

Dobson, F., R. S. Hinman, M. Hall, C. B. Terwee, E. M. Roos, and K. L. Bennell. 2012. "Measurement properties of performance-based measures to assess physical function in hip and knee osteoarthritis: a systematic review." *Osteoarthritis Cartilage* 20 (12): 1548-62. https://doi.org/10.1016/j.joca.2012.08.015.

Ebert, Jay R., Brendan Joss, Berit Jardine, and David J. Wood. 2013. "Randomized Trial Investigating the Efficacy of Manual Lymphatic Drainage to Improve Early Outcome After Total Knee Arthroplasty." *Archives of Physical Medicine and Rehabilitation* 94 (11): 2103-2111. https://doi.org/10.1016/j.apmr.2013.06.009. https://doi.org/10.1016/j.apmr.2013.06.009.

Klaber, Ianiv, Eugene Greeff, and John O'Donnell. 2019. "Compressive cryotherapy is superior to cryotherapy alone in reducing pain after hip arthroscopy." *Journal of Hip Preservation Surgery*. https://doi.org/10.1093/jhps/hnz048.

Kumar, Yogaprakash, Shih-Cheng Yen, Arthur Tay, Wang Wei Lee, Fan Gao, Ziyi Zhao, Jingze Li, Benjamin Hon, Tim Tian-Ma, Angela Cheong, Karen Koh, Yee-Sien Ng, Effie Chew, Gerald Koh, and Tianma Xu. 2015. "Wireless wearable range-of-motion sensor system for upper and lower extremity joints: A validation study." *Healthcare Technology Letters* 2: 12-17. https://doi.org/10.1049/htl.2014.0100.

Leegwater, N. C., J. H. Willems, R. Brohet, and P. A. Nolte. 2012. "Cryocompression therapy after elective arthroplasty of the hip." *Hip Int* 22 (5): 527-33. https://doi.org/10.5301/HIP.2012.9761. https://www.ncbi.nlm.nih.gov/pubmed/23112075.

MTR. 2021. "Game Ready Med4Elite." https://www.mtr-ag.ch/game-ready-de/game-ready-med4elite-tm.html.

Murgier, J., and X. Cassard. 2014. "Cryotherapy with dynamic intermittent compression for analgesia after anterior cruciate ligament reconstruction. Preliminary study." *Orthop Traumatol Surg Res* 100 (3): 30912. https://doi.org/10.1016/j.otsr.2013.12.019. https://www.ncbi.nlm.nih.gov/pubmed/24679367.

Nabiyev, V. N., S. Ayhan, P. Adhikari, E. Cetin, S. Palaoglu, and R. E. Acaroglu. 2018. "Cryo-Compression Therapy After Elective Spinal Surgery for Pain Management: A Cross-Sectional Study with Historical Control." *Neurospine* 15 (4): 348-352. https://doi.org/10.14245/ns.1836070.035. https://www.ncbi.nlm.nih.gov/pubmed/30531660.

Oesch, Peter. 2007. "Skilful use of the tape measure." *Physiopraxis* 1.

Peters, D. M., S. L. Fritz, and D. E. Krotish. 2013. "Assessing the reliability and validity of a shorter walk test compared with the 10-Meter Walk Test for measurements of gait speed in healthy, older adults." *J Geriatr Phys Ther* 36 (1): 24-30. https://doi.org/10.1519/JPT.0b013e318248e20d.

Roos, E. M., and S. Toksvig-Larsen. 2003. "Knee injury and Osteoarthritis Outcome Score (KOOS) - validation and comparison to the WOMAC in total knee replacement." *Health Qual Life Outcomes* 1: 17. https://doi.org/10.1186/1477-7525-1-17.

Stoop, Rahel, Erich Hohenauer, Dirk Aerenhouts, André Barel, Tom Deliens, Ron Clijsen, and Peter Clarys. 2020. "Comparison of two skin temperature assessment methods after the application of topical revulsive products: Conductive iButton data logger system vs contact-free infrared thermometry." *Skin Research and Technology* 00: 1-6. https://doi.org/10.1111/srt.12847.

Su, E. P., M. Perna, F. Boettner, D. J. Mayman, T. Gerlinger, W. Barsoum, J. Randolph, and G. Lee. 2012. "A prospective, multi-center, randomised trial to evaluate the efficacy of a cryopneumatic device on total knee arthroplasty recovery." *The Journal of Bone and Joint Surgery. British volume* 94-B (11_Supple_A): 153-156. https://doi.org/10.1302/0301-620X.94B11.30832. https://doi.org/10.1302/0301620X.94B11.30832.

Thienpont, Emmanuel. 2014. "Does Advanced Cryotherapy Reduce Pain and Narcotic Consumption After Knee Arthroplasty?" *Clinical Orthopaedics and Related Research®* 472 (11): 3417-3423. https://doi.org/10.1007/s11999-014-3810-8. https://journals.lww.com/clinorthop/Fulltext/2014/11000/Does_Advanced_Cryotherapy_Reduce_Pain_and_Narcotic.27.aspx.

Waterman, B., J. J. Walker, C. Swaims, M. Shortt, M. S. Todd, S. M. Machen, and B. D. Owens. 2012. "The efficacy of combined cryotherapy and compression compared with cryotherapy alone following anterior cruciate ligament reconstruction." *J Knee Surg* 25 (2): 155-60. https://doi.org/10.1055/s-0031-1299650. https://www.ncbi.nlm.nih.gov/pubmed/22928433.

Zeng, Y., W. Feng, X. Qi, J. Li, J. Chen, L. Lu, P. Deng, J. Zeng, and F. Li. 2016. "Differential knee skin temperature following total knee arthroplasty and its relationship with serum indices and outcome: A prospective study." *J Int Med Res* 44 (5): 1023-1033. https://doi.org/10.1177/0300060516655237. https://www.ncbi.nlm.nih.gov/pubmed/27596626.

17. APPENDICES

2. *Subject Information Declaration of Consent*
3. *Data collection form*
4. *Copy of proof of insurance*
5. *Advertisement*
6. *Protocol Synopsis*
7. *Employee*
8. *CV's Investigator and Sponsor*
9. *GCP Proof Investigator and Sponsor*

9. Operating manual and CE certification GR PRO 2.1