LABORATORY FOR
MOVEMENT
BIOMECHANICS

ETH
Eidgenössische Technische Hochschule Zürich
Swiss Federal Institute of Technology Zurich

Clinical Study Protocol

The influence of two modifiable stability boots on gait pattern in healthy adults

Observational study

Stability boots

Study Type:	Health-related intervention
Study Categorization:	Other Clinical Trial Category A
Study Registration:	
Study Identifier:	Stability boots
Sponsor-Investigator and Principal Investigator:	Dr. Silvio Lorenzetti Institute for Biomechanics, ETH Zürich Leopold-Ruzicka-Weg 4 8093 Zürich, Switzerland sl@ethz.ch Phone +41 44 633 6195
Study Intervention:	Stability boots
Protocol Version and Date:	Version 3.0, 08.03.2017

SIGNATURE PAGE

Study number n.a.

Study Title The influence of two modifiable stability boots on gait pattern in healthy adults

Sponsor-Investigator (Principal Investigator):

This clinical trial protocol was subject to critical review and has been approved by the Sponsor-Investigator. The information herein is consistent with
- the current risk/benefit evaluation of the intervention,
- the moral, ethical and scientific principles governing clinical research as set out in the current version of the Declaration of Helsinki, Good Clinical Practice.

Dr. Silvio Lorenzetti

Institute for Biomechanics, ETH Zürich

Leopold-Ruzicka-Weg 4

8093 Zürich, Switzerland

sl@ethz.ch

Phone +41 44 633 6195

Zh, 9.3.17 — S. Lorenzetti

Place/Date — Signature

Co-Investigator at study site:

I have read and understood this protocol and agree to conduct the trial as set out in this study protocol.

Site	Institute for Biomechanics, ETH Zürich
Co-investigator	Andris Ladner

ZH, 9.3.17 _____ _____

Place/Date Signature

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STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Dr. Silvio Lorenzetti
Study Title:	The influence of two modifiable stability boots on gait pattern in healthy adults
Short Title / Study ID:	Stability boots
Protocol Version and Date:	Version 3.0 of 08.03.2017
Trial registration:	clinicaltrials.gov: NCT03038815
Study category and Rationale	Other clinical study Category A
Background and Rationale:	After an ankle injury like distorsions, fractures or arthrodeses, or congenital defects ankle support limit the range of motion in the joint, help pain relief, control loading of the injured tissues and promote recovery of a normal gait pattern. Gait analysis is applied in orthopedics, sport science and rehabilitation. Numerous measure systems and methods enable accurate analysis of human movement
Objective(s):	Primary study objective: The study is set to describe and compare the gait analysis of two modifiable stability boots (Ortho® Tri-Phase and the VACOped®) on the standard walking parameters during two conditions (level and ramp walking) in healthy adults and draw comparisons with a control indoor shoe. Secondary study objectives: • to analyse the whole gait pattern • to examine the difficulties that occur out of ramp walking with the boots • to identify differences between the modular restriction settings in both stability boots during walking

Outcome(s):	Primary outcomes: • to analyse and compare the angle of the ankle joint in the frontal and the sagittal plane • to define ground reaction force outcome parameters: First and second peak, minima, loading and unloading rate of the ground reaction forces • to evaluate the COP on the sole Secondary outcomes: • to expound biometric data: age, gender, height, weight, shoe size • to interpret time distance parameters: gait velocity, stance/swing time, step and stride lengths
Study design:	Observational study
Inclusion / Exclusion criteria:	Inclusion criteria: • healthy • 18-45 years old • shoe size 5,6,9 or 10 Exclusion criteria: • injuries of the lower limbs • previous surgeries on the lower limbs • neuromuscular disorders • restriction in gait capabilities • current medical treatment
Study Intervention:	Ortho® Tri-Phase (stability shoe) Gait analysis (level and ramp walking) with the Ortho® Tri-Phase from Künzli SwissSchuh which has three restriction stages of Flexion/Extension (10° in the first phase and 30° in the second phase and free). At least 5 gait cycles should be recorded from each condition.
Reference Intervention:	VACOped® (stability shoe) Gait analysis (level and ramp walking) with the VACOped® from OPED which has different restriction stages of Flexion/Extension (-15°to 30°). Aim is to measure 3 of the possible restrictions. At least 5 gait cycles should be recorded from each condition.
Control Intervention:	Indoor shoe
Number of Participants with Rationale:	20 healthy participants
Study Duration:	Measurements 2 months, total 6 months
Study Schedule:	Planned start: 02.2017 Planned end: 03.2017
Investigator(s):	Dr. Silvio Lorenzetti Institute for Biomechanics, ETH Zürich Leopold-Ruzicka-Weg 4 8093 Zurich, Switzerland sl@ethz.ch Phone +41 44 633 6195
Study Centre(s):	Single-center, ETH Zurich

Statistical Considerations:	The pilot study of Bürgi & Lorenzetti 2015 was used to estimate the study sample size of 20. Significance level (α) set at 0.05 and power (1-β) at 0.8. The study will be terminated once the satisfactory power is reached with the estimated sample size. The gait analysis parameters will be described using standard descriptive statistics. Comparison between the stability boots among its outcome measures will be performed by analysis of variance tests. Significance level set at 0.05.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

LIST OF ABBREVIATIONS

AE	Adverse Event
ClinO	Clinical Trial Ordinance (KlinV)
CRF	Case Report Form
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
ICH	International Council on Harmonization
ISF	Investigator Site File
IfB	Institute for Biomechanics
KEK	Kantonale Ethik Kommision
n.a.	Not applicable
PI	Principal Investigator
ROM	Range of Motion
SAE	Serious Adverse Event
SDV	Source Data Verification
SNCTP	Swiss National Clinical Trial Portal
SOP	Standard Operating Procedure
TMF	Trial Master File

STUDY SCHEDULE

Study Periods	Registration	Gait analysis
Visit	**1**	**1**
Time (hours)	30min	2 ½ -3 h
Participant Information and Informed Consent	x	
In- /Exclusion Criteria	x	
Randomization	x	
Ortho Tri-Phase		x
VACOped		x
Indoor shoe		x
Primary outcome measures		x
Secondary outcome measures		x

1 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator (Principal Investigator)

ETH Zurich
Institute for Biomechanics
Dr. Silvio Lorenzetti
Leopold-Ruzicka-Weg 4
8093 Zurich, Switzerland
sl@ethz.ch
Phone +41 44 633 6195

As Sponsor Investigator Dr. Silvio Lorenzetti will coordinate the project and will be responsible for the quality control, education concerning GCP and the Co-investigator.

1.2 Co-Investigator

Andris Ladner

Limmattalstrasse 224

8049 Zürich

aladner@student.ethz.ch

079 575 97 57

As Co-Investigator, Andris Ladner will be responsible for helping in the recruitment of participants, data acquisition, recording and analysis. Andris Ladner does his master thesis under the supervision of Dr. Silvio Lorenzetti.

1.3 Statistician ("Biostatistician")

n.a.

1.4 Laboratory

Human Movement Laboratory
HCI D355
Institute for Biomechanics, ETH Zurich
Vladimir-Prelog-Weg 3
8093 Zürich, Switzerland

1.5 Monitoring Institution

ETH Zürich
Institute for Biomechanics
8093 Zürich, Switzerland

Since the project is a low risk study and has only a few participants an internal monitoring is sufficient.

2 ETHICAL AND REGULATOR ASPECTS

Before this study will be conducted, the protocol, the proposed participant information and consent form as well as other study-specific documents will be submitted to a properly constituted Competent Ethics Committee (CEC) in agreement with local legal requirements, for formal approval.

The decision of the CEC concerning the conduct of the study will be made in writing to the Sponsor-Investigator before commencement of this study. The clinical study can only begin once approval from the CEC has been received.

2.1 Study Registration

Seit November 2015 ist das Gesuchseinreichungsportal der Ethikkommissionen BASEC (Business Administration System for Ethics Committees) online. Die Gesuchseinreichungen und Publikationen müssen seither nicht mehr in SNCTP gemacht werden, sondern erfolgen direkt im BASEC. Eingereichte Informationen werden nach der Bewilligung eines klinischen Versuches von BASEC an SNCTP übergeben. (http://kofam.ch/de/studienportal/klinische-versuche-registrieren/)

The study will be registred on clinicaltrials.gov
Identifier: NCT03038815

2.2 Categorization of the Study

Category A: The health-related study intervention entails only minimal risks and burdens or is recognized as standard in guidelines prepared in accordance with internationally accepted quality criteria.

2.3 Competent Ethics Committee (CEC)

Approval from the appropriate constituted Competent Ethics Committee is sought for the clinical trial. The reporting duties and allowed time frame are respected. No substantial amendments are made to the protocol without prior CEC approval, except where necessary to eliminate apparent immediate hazards to study participants. Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.9.

2.4 Ethical Conduct of the Study

The study will be carried out in accordance with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, and Swiss competent authority's requirements.

CEC will receive annual safety and interim reports and be informed about non-substantial amendments, the course of the study, and the study stop/ end in agreement with local requirements.

2.5 Declaration of Interest

There is no financing for this project planned.

2.6 Participant Information and Informed Consent

The investigator must explain to each Participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant must be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment.

The participant must be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All Participants for this study will be provided a participant information sheet and a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study.

The participant information sheet and the consent form will be submitted with the protocol for review and approval for the study by the CEC. The formal consent of a participant, using the approved consent form, must be obtained before that participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

2.7 Participant Privacy and Confidentiality

The investigators are liable to treat the entire information related to the study and the compiled data strictly confidentially. Any passing-on of information to persons that are not directly involved in the study must be approved by the owner of the information.

Data generation, transmission, archiving and analysis of personal data within this study, strictly follows the current Swiss legal requirements for data protection. Prerequisite is the voluntary approval of the Participant given by signing the informed consent prior start of participation of the clinical trial.

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Participant's confidentiality will be further ensured by utilizing participant identification code numbers to correspond to treatment data in the computer files.

Data generated as a result of this study are to be available for inspection on request by the monitors and by the CEC.

2.8 Early Termination of the Study

Each subject has the right to withdraw from the study at any time without prejudice. If a subject withdraws, the reason(s) will be documented

The Sponsor-Investigator may discontinue the study prematurely according to certain circumstances:

- ethical concerns,
- insufficient participant recruitment,
- when the safety of the participants is doubtful or at risk, respectively,
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise,
- early evidence of benefit or harm of the experimental intervention

2.9 Protocol Amendments

Substantial amendments (significant changes) are only implemented after approval of the CEC.

Significant changes to be authorised by the CEC are the following:

- changes affecting the participants' safety and health, or their rights and obligations;

- changes to the protocol, and in particular changes based on new scientific knowledge which concern the trial design, the method of investigation, the endpoints or the form of statistical analysis;
- a change of trial site, or conducting the clinical trial at an additional site; or
- a change of sponsor, coordinating investigator or investigator responsible at a trial site.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human participants may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible.
All Non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

3 INTRODUCTION

3.1 Background and Rationale

In both daily grind and sports the ankle joint is one of the most commonly injured joint in the human body (Best et al., 2011) (Morrison & Kaminski, 2007) (Van Rijn et al., 2008). In general 15% to 20% of all sporting injuries are associated with the ankle in which 75% are lesions of the ligaments. After an ankle injury like distorsions, fractures or arthrodeses, or congenital defects ankle support limit the range of motion in the joint, help pain relief, control loading of the injured tissues and promote recovery of a normal gait pattern (Kerkhoffs et al., 2002). Injuries of soft tissue like ankle ligament injuries were linked with different healing phases. First there is an inflammation phase for 1 to 5 days. Followed by the primary healing phase (5 to 28 days) with symptoms like angiogenesis, proliferating fibroblasts and collagen production. A remodelling phase terminals the rehabilitation process. The ligament stability recovers after the "form follows function" principle. The several phases are individually different in their duration and are overlapping by each other. The complete healing process last 16 to 50 weeks. Therefore, an ideal rehabilitation of an ankle ligament injury should give respect to these healing periods (Best et al., 2011). The stability boots to be tested in this thesis can be individually adapted. The modifiable ankle support has according to the healing phases different stages and restricts the joint in the two planes (frontal and sagittal) (Künzli, 2015; Oped, 2016)
So far there have not been conducted gait analysis with a modifiable stability boot.

Locomotion is reproducible and follows the same physiological terms in all healthy human as it is controlled by a neuronal network known as the central pattern generator (Guertin, 2009). Gait analysis is applied in orthopedics, sport science and rehabilitation. Numerous measure systems and methods enable accurate analysis of human movement (Kramers-de Quervain et al., 2008).

When walking on levelled overground the ankle joint angle does not varying much and makes it a simple aim for orthosis and stability boot designs (Hansen et al., 2004). Human gait occurs not only on levelled ground, therefore walking uphill or downhill a ramp would be interesting to examine. Slope walking has been correlated with altering typical gait pattern of level walking of a healthy human (Gottschall et al., 2011). Kawamura et al. (1991) and Sun et al. (1996) have found that the cadence and the stride length change during hill walking. Sun et al. (1996) found that a product of a decrease in step frequency and an increase in step length account for a decreased speed in uphill walking. In comparison, during downhill walking, shorter step length due to reduction in friction was detected (Gottschall et al., 2011). Especially when walking uphill the adaptions were a result of the changes in the ankle-foot complex through plantarflexion and

dorsiflexion of the ankle (Hansen et al., 2004). Lay et al., however, did not find any significant difference in stride length between level walking and hill conditions.

The primary objective is set to describe and compare the three-dimensional kinematics and kinetics of two modifiable stability boots (Ortho® Tri-Phase and the VACOped®) on the standard walking parameters during two conditions (level and ramp walking) in healthy adults and draw comparisons with an indoor shoe.

3.2 Study Intervention and Indication

This is a study investigating healthy participants with during level and ramp walking and analysing the ankle movement with gait analysis with minimal risks to the participants.

3.3 Clinical Evidence to Date

Bürgi & Lorenzetti (2015) developed both, a machine and a fast testing method to compare prototypes of stability boots fast and objective with each other. Thus, a final prototype was developed and was tested with a gait analysis (only level walking) and compared with the already in existence standard model. The aim was to compare the stabilization effect of the final prototype stability boot with its two ankle joint restriction stages with the standard model.

Now the modified final product of this boot is in the market. The stability boot has three ankle joint restriction stages and it will be tested against the proven VACOped®.

3.4 Justification of Study Intervention

New findings could assist in further development of stability boots.

3.5 Explanation for Choice of Comparator Intervention

Comparing two stability boots.

3.6 Risk / Benefits

Risk:
No more than minimum risk for study participants. No risks are associated with measurements of ground reaction forces and skin marker positions during gait analysis. Gait analysis is a standard assessment procedure and neither physical nor psychological risks are known. The skin markers are small (1-2 cm diameter) and very light, and they do not affect the participants gait or well-being. Should a participant feel uncomfortable or exhausted, the procedure can be discontinued anytime

Benefit:
New findings could assist in further development of stability boots. The gait analysis provides exact results and new findings about gait with stability boots in daily walking conditions. Participants may have information about their gait.

3.7 Study Population

The study population consists of healthy persons between 18 and 45 years old.

4 STUDY OBJECTIVES

4.1 Overall Objective

The purpose of this project is to describe and compare the gait analysis parameters of healthy adults wearing stability boots, tracking mounted skin markers and acquiring force data using force plates.

4.2 Primary Objective

The study is set to describe and compare the three-dimensional kinematics and kinetics of two modifiable stability boots (Ortho® Tri-Phase and the VACOped®) on the standard walking parameters during two conditions (level and ramp walking) in healthy adults and draw comparisons with the control intervention; an indoor shoe.

4.3 Secondary Objectives

- to analyse the whole gait pattern
- to examine the difficulties that occur out of ramp walking with the boots
- to identify differences between the modular restriction settings in both stability boots during walking

4.4 Safety Objectives

n.a.

5 STUDY OUTCOMES

5.1 Primary Outcome

The primary outcome of this study is the difference between the stability boots and their different restriction settings during level and ramp walking.

This project is set to:

- analyse and compare the angle of the ankle joint in the frontal and the sagittal plane
- to define ground reaction force outcome parameters: First and second peak, minima, loading and unloading rate of the ground reaction forces
- to evaluate the COP on the sole

5.2 Secondary Outcomes

This project is set to:

- to expound biometric data: age, gender, height, weight, shoe size

- to interpret time distance parameters: gait velocity, stance/swing time, step and stride lengths

5.3 Safety Outcomes

n.a.

6 STUDY DESIGN AND COURSE OF STUDY

6.1 General Study Design and Justification of the Design

An observational, open trial study will be planned. Healthy subjects will be recruited. They will be analysed during level and ramp walking with two different stability shoes and an indoor shoe.

- 20 healthy subjects will be recruited in total.
- The stability boot Ortho® Tri-Phase (Künzli SwissSchuh) will be the intervention. It has three phases of restriction of the ankle joint in the sagittal plane.
- The reference intervention will be the stability boot VACOped® (OPED AG). It has different restriction stages of Flexion/Extension (-15° to 30°).
- The control intervention will be an indoor shoe.
- The duration of the measurements will be 2 months.
    - Planned start: 02.2017
    - Planned end: 03.2017

Ground reaction forces: Ground reaction forces are simultaneously measured with the use of 5 force plates mounted flush in the floor and two forces plates on the ramp (Kistler, Instrumentation, Winterthur, Switzerland). The force plates are decoupled from the surrounding floor, which enables measurements of force which are undisturbed by the rolling cart. Force plate data is improved by a special correction algorithm to enhance the accuracy of the path of the centre of pressure.
Stance phase detection: Heel strike and toe off are defined based on ground reaction forces captured using the force plates.

Motion Capture: The 3D motion analysis system used is a VICON MX system (Oxfords Metrics Group, UK). It consists of 9 fixed and 3 movable MX40 motion-capture cameras with a resolution of 2352x1728 pixels and a capture frequency of 100Hz as well as of 6 fixed and 4 movable MXT160 motion-capture cameras with a resolution of 16 Megapixels and a capture frequency of 120 Hz. This adds up to 15 fixed cameras and 7 movable cameras. The instrumental error of marker position is ≤ 1mm (root mean square error).
The used marker set is based on the marker set of the University of Denver, consisting of 45 skin markers with a diameter of 14mm. This marker set will be completed by additional markers of the 53 standard marker set of the Institution for Biomechanics, ETH Zurich to a total of 62 mounted skin markers. Therefore it is based on redundant marker point clouds and functionally estimated joint centres, respectively axis (List et al., 2012)

The test procedure consists of six trials that just include the motion capture system, namely a standing trial in an anatomic upright position and a calibration motion as well as four basic motion tasks to define functional estimated joint axis, respectively centers (each performed

twice). All trials of level and ramp up and down walking are assessed simultaneously by the motion capture systems as well as force plates.

For each of the gait conditions (ramp up, ramp down and level walking) and each restriction of the stability boots (10°, 30° and 45°/free) the subjects have to perform five valid trials. In total there are at least 21*5 trials. A gait trial is considered valid, when the foot is in the field of view of the image intensifier during stance and swing phase and the force plate is hit for level and ramp gait. Mean and standard deviation of the five trials will be calculated.

Motion Tasks:
- Level walking
- Ramp up walking
- Ramp down walking

6.2 Study Duration and Study Schedule

The total duration of the study will be 6 months.
Start: 10.10.16
End: 10.04.17
Measurements: February 2017 until March 2017
Data analysis: February 2017 until April 2017

6.3 Methods of Minimizing Bias

6.3.1 Randomization

If the participant has to wear the VACOped® or the Ortho Tri-Phase® first will be randomized. Through technical reasons the indoor shoe cannot be randomized.

6.3.2 Blinding Procedures

No blinding procedure are performed in this study.

6.4 Unblinding Procedures (Code break)

n.a.

7 STUDY POPULATION

7.1.1 Inclusion Criteria

Participants fulfilling all of the following inclusion criteria may be enrolled in the study:

Inclusion criteria:

- Healthy
- 18-45 years old
- shoe size 5,6,9 or 10

7.1.2 Exclusion Criteria

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

Exclusion criteria:

- injuries of the lower limbs
- previous surgeries on the lower limbs
- neuromuscular disorders
- restriction in gait capabilities
- current medical treatment

7.2 Recruitment and Screening

Enrollment is planned for a period of 2 months. Direct recruitment of potential study participants, contact between the study team and potential subjects in person. Volunteers giving written informed consent will be assessed during the visit at the institute of biomechanics.

There will be no payment given as compensation for time and effort of the participants. To ensure gaining baseline data for each gender the aim is to enroll ten men and ten women.

7.3 Assignment to Study Groups

Not applicable. Data will only be acquired in only one study group. All participants will be tested in all three interventions.

7.4 Criteria for Withdrawal/ Discontinuation of Participants

Each subject has the right to withdraw from the study at any time without prejudice. If a subject withdraws, the reason(s) will be documented.

Should a participant feel uncomfortable or exhausted during the measurements, the procedure can be discontinued anytime. In case of withdrawal during the measurement or withdrawal after the measurement, the data still will be evaluated so the study doesn't lose its value. Although the data and the material will be anonymised which means that anonymization key will be deleted for this subject so nobody can track down the data to the according subject. In case of too much invalid trials due to too short step length or similar unforeseen incidents which lead to insufficient amount of data, the Sponsor-Investigator will initiate the recruitment of an additional subject to prevent the loss of the study's value.

8 STUDY INTERVENTION

8.1 General Information

For each subject a gait analysis involves: 5 valid trials on level and on ramp walking with the study intervention, the reference intervention and the control intervention.

8.1.1 Study Intervention

Study Intervention A

The stability boot Ortho® Tri-Phase is a product of Künzli SwissSchuh AG.

8.1.2 Reference Intervention

Study Intervention B

The stability boot VACOped® from OPED AG.

8.2 Administration of Study Intervention and Reference Intervention

8.2.1 Study Intervention

The Ortho® System ensures, according the producer, right amount of stability. Through the calculated softness of the boot mobility is warranted. The boot assures an early functional and early weight bearing of the injured foot. The stability boot Ortho® Tri-Phase is a product of Künzli SwissSchuh and a postoperative/conservative therapy for ankle injuries as distortion, arthrodesis, chronic ankle instability or calcaneus and ankle fractures. A modular joint should ensure a restriction of the ankle joint. The boot can be individually adapted. The modular extractable ankle support has according to the three healing phases three different stages and restricts the joint in the two planes (frontal and sagittal). In the first phase the boot should restrict the range of motion in the ankle joint 10°, in the second phase 30° and in the third there is no limitation. During all phases the boot limits the Inversion/Eversion movement in the frontal plane. Due to wearing the new stability boot in pairs a healthy gait symmetry and the preservation of body statics is ensured. For each of the gait conditions (ramp up, ramp down and level walking) and each restriction of the stability boot (10°, 30° and free) the subject has to perform five valid gait trials. (Künzli, 2015)

8.2.2 Reference Intervention

The VACOped® dynamic vacuum ankle orthosis product of OPED and treats like the OTP ankle fractures, metatarsal and calcaneus fractures, distortions, prosthetics, arthrodesis but additionally it is a therapy for achilles tendon ruptures. OPED promises that an early weight bearing of the injured foot will be possible. The boot gives option to adapt the range of motion of the sagittal plane from -15° to +30°. It should shorten the recovery time and therefore early mobility will be ensured. Moreover, an earlier risk free weight bearing of the foot counteract atrophy and ensures a soon return to work. The developed vacuum cushion adapts to individual patients anatomy and can be modified to fit swelling and atrophy. Other than the Ortho Tri-Phase® the VACOped® is worn only on one foot. For each of the gait conditions (ramp up, ramp down and level walking) and each restriction of the stability boot (10°, 30° and 45°) the subject has to perform five valid gait trials. (Oped, 2016)

8.2.3 Control Intervention

The control intervention is an indoor shoe. It will serve as a reference to participants normal gait parameters. Every subject does have his own pair of indoor shoe, which it will bring to the visitation.

8.2.4 Modification of Interventions

n.a.

8.3 Compliance with Intervention

n.a.
The observer knows which intervention the subject wears.

8.4 Data Collection and Follow-up for Withdrawn Participants

Each subject has the right to withdraw from the study at any time without prejudice. If a subject withdraws, the reason(s) will be documented.

Should a participant feel uncomfortable or exhausted during the measurements, the procedure can be discontinued anytime. In case of withdrawal during the measurement or withdrawal after the measurement, the data still will be evaluated so the study doesn't lose its value. Although the data and the material will be anonymised which means that anonymisation key will be deleted for this subject so nobody can track down the data to the according subject. In case of too much invalid trials due to too short step length or similar unforeseen incidents which lead to insufficient amount of data, the Sponsor-Investigator will initiate the recruitment of an additional subject to prevent the loss of the study's value.

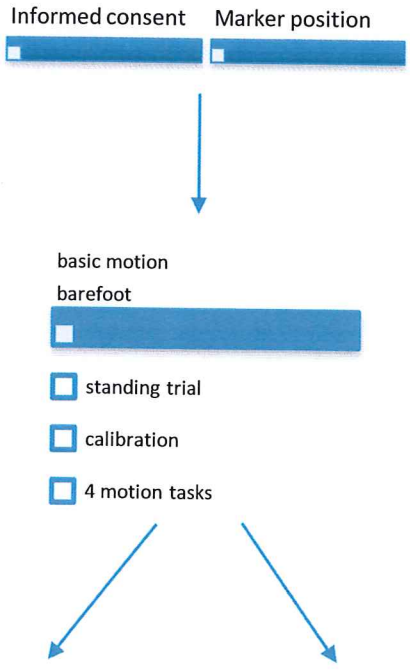
8.5 Concomitant Intervention(s)

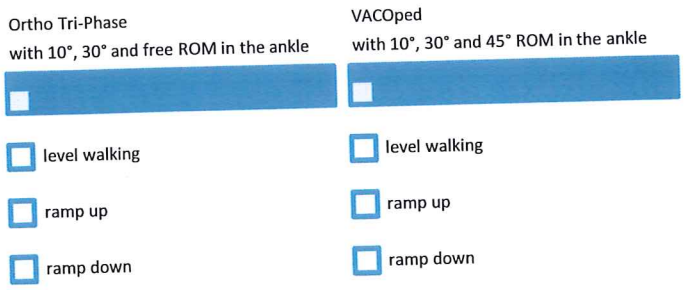
n.a.

9 STUDY PROCEDURES

This study involves one dynamic data acquisition synchronized optical motion capture with measurements of ground reaction forces during level walking and ramp walking. The expected total time involvement for each participant maximally adds up to 3 hours.

9.1 Study Flow Chart/Table of Study Procedures and Assessments





9.2 Assessments of Outcomes

9.2.1 Assessment of Primary Outcome

Optical motion capture by means of passive reflective skin markers:
The optical motion capture system used in this project corresponds to a conventional motion capture system, i.e. Vicon motion analysis system (Oxford Metrics Group, UK). The method consists in attaching 62 small passive reflective markers on the skin using hypoallergenic tape. Up to 20 fixed and 12 movable cameras register the 3D coordinates of the markers during movement with a capture frequency of up to 2000Hz. The markers are small (1-2cm diameter) and very light, and they do not affect the participants gait or well-being.
The kinematic data of the skin markers will be reconstructed using Vicon Nexus 1.7.1. The markers have to be visible in at least two cameras for reconstruction. Two models, the subject model and a model for the moving fluoroscope will be used. Automatic labeling as well as manual correction will be applied. All relevant gait events will be set. This means more gait events will be set than necessary for defining the 5 valid trials. The "heel strike" events will be set at the first frame the force vector appears on the force plate and the "toe off" events at the first frame the force vector disappears. The force vector is displayed if the force exceeds the 25 N threshold. The Data will be saved as a C3D-file.

Ground reaction force measurements:
Ground reaction forces, i.e. the forces that the subject exerts with the foot to the ground, are measured by six force plates (Kistler Instrumentation, Switzerland) embedded in the ground of the movement analysis laboratory. Additionally, two mobile force plates are installed in a staircase for the measurement of the stair activity. Force measurements and motion capture take place simultaneously and are at all times synchronised.
The origin of the lab coordinate system is equal to the origin (mid-point) of the third force plate B3. Force data as well as the resulting center of pressure (COP) will be described in each force plate's coordinate system. The exact origins and orientations of the mobile force plates will be calculated using the positions of four calibration markers. All force data will be transformed from the respective force plate coordinate system to the lab coordinate system and saved as a C3D-file with the corresponding kinematic data.
COP values will be corrected by our in-house calibration procedure performed for each force plate [15-17]. The corrected COP values are only estimated for vertical forces larger than 100N. Further data processing of the generated C3D-files and text-files to conduct the calculation of the outcome parameters will be done using Matlab (R2012a, The MathWorks, Inc., Natwick, USA).

Ground Reaction Force Outcome Parameters:

First and second peak (Fz2, Fz4), minima (Fz3), loading (bn) and unloading rate (en) of the ground reaction forces are defined according to Stacoff et al. (2007) (Figure 1).

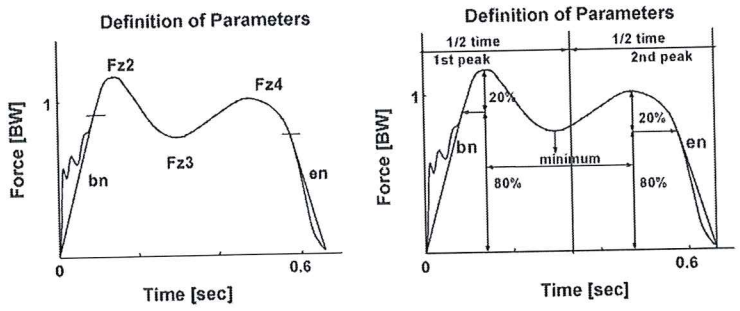


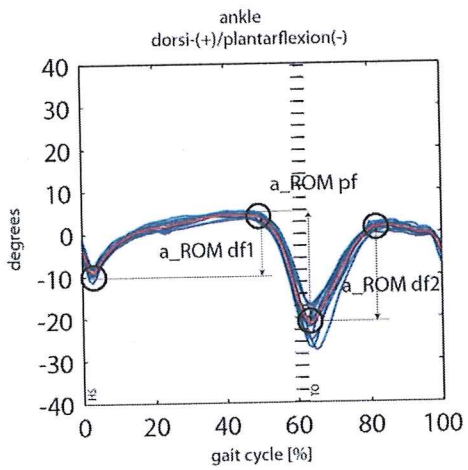
Figure 1: Definition of ground reaction force parameters (Stacoff et al., 2007)

Time-Distance-Parameters: For level walking gait velocity is defined as the mean horizontal velocity of the sacrum marker over the whole gait cycle. For ramp gait velocity is described as the mean horizontal as well as vertical velocity of the sacrum marker over the whole gait cycle.

Motion Capture Outcome Parameters:

Skin marker based ankle, knee and hip rotations are described with respect to functionally estimated joint coordinate systems (distal relative to proximal segment).

Joint	Plane	Parameter
Ankle	sagittal	- *a_ROM df1*
		- *a_ROM pf*
		- *a_ROM df2*
	frontal	- *a_ROM invev*
	transverse	- *a_ROM adab*

a_ROM df1 *a_ROM pf* *a_ROM df2*		
	a_ROM df1	ROM between peak of maximal plantarflexion and peak of maximal ankle [°]

		dorsiflexion in stance	
	a_ROM pf	ROM between peak of maximal ankle dorsiflexion in stance and peak of maximal plantarflexion beginning of swing	[°]
	a_ROM df1	ROM between peak of maximal plantarflexion beginning of swing and peak of maximal ankle dorsiflexion in swing.	[°]
a_ROM adab	Range between the maximal and the minimal reached values of ankle adduction/abduction at any time. [°]		
a_ROM invev	Range between the maximal and the minimal reached values of ankle inversion/eversion at any time. [°]		

Table 1: Motion capture outcome parameters

9.2.2 Assessment of Secondary Outcomes

Every subject's weight and height will be measured at the day the research will be conducted. During the acquisition of the daily activities two video cameras are used to record the subject's execution of the task. This is done to retrace the motion in case of odd results to assure no false data will be integrated in the study. This is the only use for these videos and they will be stored and anonymised as all other data.

9.2.3 Assessment of Safety Outcomes

n.a.

9.2.3.1 Serious Adverse Events

n.a.

9.2.3.2 Laboratory Parameters

n.a.

9.2.3.3 Vital Signs

n.a.

9.2.4 Assessments in Participants who Prematurely Stop the Study

This study only involves one visit for each participant with a gait analysis during dynamic activities (total acquisition time up to 4 hours). Based on our experience, we do not anticipate early termination if a subject complies with all the inclusion/exclusion criteria and has given written consent to participate in the study. Should a participant feel uncomfortable or exhausted during the dynamic video-fluoroscopic measurements, the procedure can be discontinued anytime.

9.3 Procedures at Each Visit

9.3.1 Visit 1

- Participant Information and Informed Consent
- Change into shorts, t-shirt
- Completion of the biometric data by measuring weight and height
- Place 62 small passive reflective markers on the skin using hypoallergenic tape

according to standard gait analysis protocol

The test procedure, consisting of basic motion tasks and 21 dynamic trials (dynamic trials) assessed simultaneously with the motion capture systems and the force plates.

For each of the gait conditions (ramp up, ramp down and level walking) and each restriction of the stability boots (10°, 30° and 45°/free) the subjects have to perform five valid trials. In total there are at least 21*5 trials. A gait trial is considered valid, when the foot is in the field of view of the image intensifier during stance and swing phase and the force plate is hit for level and ramp gait.

Basic motion tasks (each task performed twice):

- Standing trial in an anatomic upright position
- Calibration (Standing in upright position, followed by free movement of legs and arms)
- Four motion tasks to functionally define joint axes and joint centers: dorsi/plantar flexion motion of the ankle, inversion/eversion motion of the ankle, flexion/extension motion of the knee, varus/valgus angle of the knee, hip circumduction (List et al., 2012)

Dynamic trials (five valid gait cycles for each activity):

- Level walking
- Ramp up walking
- Ramp down walking

10 SAFETY

The Sponsor's SOPs provide more detail on safety reporting.

During the entire duration of the study, all serious adverse events (SAEs) that may be causally related to the study intervention are collected and documented in source documents. Reportable events are recorded in the case report form (CRF). Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period.

10.1 Definitions

Adverse events

Adverse events (AEs) are defined as any untoward medical occurrence in a patient or clinical investigation participant after the intervention and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any favorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the intervention, whether or not related to the intervention. An AE may also consist of a new disease, an exacerbation of a pre-existing illness or condition, a recurrence of an intermittent illness or condition, a set of related signs or symptoms, or a single sign or symptom.

Serious Adverse Event

A serious adverse event is defined as any event which:

- requires inpatient treatment not envisaged in the protocol or extends a current

- hospital stay;
- results in permanent or significant incapacity or disability;
- is life-threatening or results in death; or
- causes a congenital anomaly or birth defect.

10.2 Recording and Assessment of Serious Adverse Events

The investigator has the responsibility for SAE identification, documentation, and assessing the causal relationship study intervention.

All SAEs will be fully documented in the appropriate CRF. For each SAE, the investigator will provide the onset, duration, treatment required, outcome and action taken with regard to the study intervention.

The assessment by the investigator with regard to the study intervention relation is done according to the following definitions:

Unrelated	• The event started in no temporal relationship to the medical intervention applied and • The event can be definitely explained by underlying diseases or other situations.
Related	• The event started in a plausible temporal relationship to the medical intervention applied and • The event cannot be definitely explained by underlying diseases or other situations.

10.3 Reporting of Serious Adverse Events

Safety measures that must be taken during conducting the measurement to protect the study participant as well as the underlying circumstances will be reported within seven days by the Sponsor-Investigator to the Ethics Committee.
In case of appearance of a safety related event concerning one of the recruited subjects while conducting the measurement, it will be discontinued immediately. The occurrence of a safety related event and its connection to the Data collection will be reported within seven days by the Sponsor-Investigator. Furthermore the Sponsor-Investigator suggests a further proceeding to the ethics committee.
The Sponsor-Investigator will report the completion or the abortion of the study to the ethics committee within 90 days.

If, in the course of a clinical trial, serious adverse events occur in participants in Switzerland, and it cannot be excluded that the events are attributable to the intervention under investigation, the investigator must report these events:

- to the KEK **within 15 days**.

Safety and protective measures
If immediate safety and protective measures have to be taken during the conduct of this clinical trial, the investigator must notify the KEK of these measures, and of the circumstances necessitating them, **within 7 days**.

First aid will be provided from the investigators and the following report procedure will be conducted:

Reporting an emergency at ETHZ

Where? Location of the accident (building, floor, room no.)

What? Type of emergency situation

Who? Name of the person reporting/contact details

When? Time of the incident

How many? Number of patients (and their injuries)

What else? Any other imminent hazards

Incident

Someone has been injured or needs medical attention. The kind of incident requires help from the First Aid Team or healthcare professionals.

What to do

1. **Alert the Emergency Desk** (cf. reporting model)
   From internal phones 888
   From external phones 044 342 11 88
   The Emergency Desk will mobilise the First Aid Team and, if need be, call an ambulance.
2. **Perform first aid**
   Assist the First Aid Team.
3. **Direct the ambulance**
   If an ambulance is called, helpers need to wait for it at the agreed location to guide it in and show the paramedics the quickest route to the casualty/casualties.

What else?

If you report an incident to the external emergency services, **make sure to notify the Emergency Desk too**. As a hub for emergencies at ETH Zurich, it must be informed of all incidents.

Minor injuries

Bandage material is provided in the corridors and first-aid stations in all ETH-Zurich buildings. The storage sites are marked with a white cross on a green background.

Uncertainty about the severity of an injury or complications

Consult the doctor.

Eye injuries (chemical spatter etc.)

Consult the doctor immediately.

Annual Safety Report

All SAEs will be summed up in the **annual safety report (ASR)** and submitted to the KEK. ASR shall contain:

- A summary of events including severity and causal relationship to the intervention and on the safety of participants.
- The accompanying letter provided with the Annual Safety Report should contain a short summary of the status of the clinical trial in Switzerland (number of centers open/closed, number of patients recruited/recruitment closed, and number of SAEs).

10.4 Follow up of (Serious) Adverse Events

Participants terminating the study (either regularly or prematurely) with

- reported ongoing SAE, or
- any ongoing AEs of laboratory values or of vital signs being beyond the alert limit

will not return for a follow-up investigation.

11 STATISTICAL METHODS

In order to obtain reasonable levels of both Type I and Type II errors, the required number of subjects (sample size) will be estimated using the power analysis approach.

11.1 Hypothesis

The null hypothesis will be that the kinematics in terms of range of motion of flexion/extension and the inversion/eversion of the ankle will not differ between the Ortho Tri-Phase® (Künzli SwissSchuh AG) and the VACOped® (OPED AG). The alternative hypothesis will be that the kinematics in terms of range of motion of flexion/extension and the inversion/eversion of the ankle will differ between the Ortho Tri-Phase® (Künzli SwissSchuh AG) and the VACOped® (OPED AG).

11.2 Determination of Sample Size

The pilot study of Bürgi & Lorenzetti (2015) was used to estimate the study sample size of 20. The mean ankle angle of the prototype with its first ankle joint restriction stage was 16.5 and with its second stage 18.6. Significance level (α) set at 0.05 and power ($1-\beta$) at 0.8.
σ is the expected standard deviation of 2.7.

The study will be terminated once the satisfactory power is reached with the estimated sample size.

11.3 Planned Analyses

The statistical analyses will be performed using SPSS statistical analysis software. The level of significance for all analyses will be set to P=0.05.

11.3.1 Datasets to be Analyzed, Analysis Populations

The acquired data of all subjects will be included in the analysis. The kinematics data will be divided into 9 subgroups according to the motion tasks that are level walking, ramp up walking and ramp down walking and the three various joint restrictions of the ankle.

11.3.2 Primary Analysis

The primary analysis in this study will be the power-analysis conducted with the null hypothesis, the error of the first kind α=0.05, the error of the second kind β=0.20 and consequently the power 1- β=0.80.
The gait analysis parameters will be described using standard descriptive statistics. Comparison between the stability boots among its outcome measures will be performed by analysis of variance tests.

11.3.3 Secondary Analyses

n.a.

11.3.4 Interim Analyses

n.a.

11.3.5 Safety Analysis

n.a.

11.3.6 Deviation(s) from the Original Statistical Plan

Any deviations from the original statistical plan will be described and justified in protocol and in the final report to the CEC.

11.4 Handling of Missing Data and Drop-Outs

Based on our experience in clinical and biomechanical gait analysis, we do not anticipate missing data or drop-outs, once a participant has given written informed consent and complies with all the inclusion/exclusion criteria of this pilot study. In case of too much invalid trials due to too short step length or similar unforeseen incidents which lead to insufficient amount of data, the Sponsor-Investigator will initiate the recruitment of an additional subject to prevent the loss of the study's value.

12 ELIGIBILITY OF THE PROJECT SITE(S)

New findings could assist in further development of stability boots. The gait analysis provides exact results and new findings about gait with stability boots in daily walking conditions.

Movement Biomechanics Lab, Institute for Biomechanics, ETH Zurich
The human movement analysis laboratory at the Institute for Biomechanics at the ETH has a motion capture systems including a total of 32 Vicon motion capture cameras. Furthermore, the laboratory has six ground-embedded and two mobile force plates, which record with a sampling frequency of 2000 Hz. All force plates were manufactured by Kistler (Winterthur, Switzerland) and have no contact with the surrounding floor. The ground-embedded force plates are installed on a concrete pillar, which is constructed onto the basement building. A damping material under the pillar reduces the vibrations from the surrounding environment. All systems are available for the proposed study.

The human movement analysis laboratory at the Institute for Biomechanics at the ETH is already temporarily reserved for the conduct of the present study.

13 DATA QUALITY ASSURANCE AND CONTROL

The Sponsor-Investigator is implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions to ensure that trials are conducted and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

Monitoring and Audits will be conducted during the course of the study for quality assurance purposes.

13.1 DATA HANDLING AND RECORD KEEPING

The collection, transfer, storage and processing of personal data within this study are in accordance with applicable Swiss data protection regulations. Data protection procedures will comply with national and EU legislation, and in particular with the European data protection Directive 95/46 and Regulation 2001/45 of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data.

13.1.1 Case Report Forms

The protocol of the study outline will be handed in as a measuring report ("Messprotokoll") and a SAE CRF.

All data files (mat-files, c3d-files) will be stored electronically. The clinical data and the measurement protocol are stored in hardcopy form and in mat-files. The raw data generated from the force plate and the motion capture system is stored in c3d-files. All the primary and secondary outcome parameters will be read out from the mat-files and thanks to the saved raw data these parameters are reproducible.

13.1.2 Specification of Source Documents

Source data includes all information in original records, observations, or other activities in this research study necessary for the reconstruction and evaluation of the research. The source data of this study includes

- Signed Informed Consent Forms to participate in this study
- Optical motion capture data from static, functional assessment
- Optical motion capture data during motion tasks
- Ground reaction forces during motion tasks.

All source data will be kept at the IfB, ETH Zürich, to document the existence of the study participants as well as the acquired data.

13.1.3 Record Keeping / Archiving

All materials pertaining to the investigation will be documented by the Sponsor-Investigator Dr. Silvio Lorenzetti, sorted and kept confidentially and anonymously in closed archives at the IfB of the ETH Zürich. The Investigators will maintain study essential documents including source data and related study documentation for a period of not less than 10 years after end or termination of the study. All case report forms and other data (including without limitation, written, printed, graphic, video and audio material, and information contained in any computer database or computer readable form) and other results including Intellectual Property created or developed during the course of the Study (the "Data") shall be the property of Institution, which may utilise the Data in any way it deems appropriate, subject to and in accordance with applicable privacy laws and the terms of this Agreement. The video data can only be taken with recording the face. Nobody but the investigators have access to this video data.

13.2 Data Management

Data backup and archiving: Data is backed up to ETH internal infrastructure; therefore there is no off-site storage outside the ETH domain. Server / directory access rights are maintained across the backups and archives, therefore there is no possibility for a non-authorised individual to reconstruct the data.
Server as well as backup is maintained by IT services group of the department HEST (Tivoli Storage Manager – IBM Backup software). Storage admins have only restricted access needed to provide the service.
Only Silvio Lorenzetti as approved Sponsor-Investigator will have access to the files with personal information and with the code linking the data to a specific participant. The files with personal information and with the code linking to a specific participant will be kept behind at least two keys (e.g. computer password, and locked office or data server; or locked door and locked file cabinet). The passwords will be changed regularly (every six months maximum).
Data (including source documents) will be made fully available to the ethics committee upon request for the purpose of monitoring, audits or inspection.

13.3 Routine Monitoring

Since the project is a low risk study and has only a few participants an internal monitoring is sufficient. The monitoring will be conducted through Barbara Postolka (Institute Biomechanics ETH Zürich Doktorat, qualified GCP)

All original data including all participant files, progress notes must be available for monitoring. The monitor will review all or a part of the protocol of the study outline ("Messprotokoll") and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents.

13.4 Audits and Inspections

This study only involves one visit for each participant, no procedure for auditing trial conduct is implemented. The Investigators confirm that the source data/documents are accessible to inspection by CEC under the accepted conditions of strict confidentiality. The Investigators will allocate his/her time to answer study-specific questions during inspections.

13.5 Confidentiality, Data Protection

Any personal information from participants will be treated with strict confidence. All personal data acquired in the scope of this study will be stored anonymously in the IfB archives through participant study ID numbers. The acquired data will be used from the IfB for statistical analysis and scientific purposes. Information may be recorded on paper and on a computer database at the hospital as well as at the Institute for Biomechanics, ETH Zurich. The data will be encoded ; name and address will be removed and subjects will only be identified by a study number and four letters.

The Investigators agree to allow the project coordinator direct access to all relevant documents and to allocate his/her time and the time of his/her staff to discuss findings and any relevant issues.

13.6 Storage of Biological Material and Related Health Data

n.a.

14 PUBLICATION AND DISSEMINATION POLICY

After the statistical analysis of this trial the sponsor will make every endeavor to publish the data in a medical journal.

15 FUNDING AND SUPPORT

This study is sponsored by the ETH Zürich

15.1 Funding

15.2 Other Support

Künzli SwissSchuh has provided both, the Ortho® Tri-Phase and the VACOped®.

16 INSURANCE

Insurance is covered by "Versicherung für klinische Versuche und nichtklinische Versuche" by Zürich Versicherungs-Gesellschaft AG (Policy no.: 14.970.888).

Any damage developed in relation to study participation is covered by this insurance. So as not to forfeit their insurance cover, the participants themselves must strictly follow the instructions of the study personnel. Participants must not be involved in any other medical treatment without permission of the principal investigator (emergency excluded). Medical emergency treatment must be reported immediately to the investigator. The investigator must also be informed instantly, in the event of health problems or other damages during or after the course of study treatment.

The investigator will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to study participation. All involved parties will keep the patient data strictly confidential.

A copy of the insurance certificate will be placed in the Investigator's Site File.

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18 APPENDICES