Clinical Study Protocol

Feasibility and cost description of intensive rehabilitation involving new technologies in patients with sub-acute stroke:A multicenter single arm trial of the Swiss RehabTech Initiative

Short title: New technologies in the rehabilitation of chronic stroke

Study Type:	Health-related intervention
Study Categorization:	Other Clinical Trial Category A
Study Registration:	U.S. National library of Medicine (https://clinicaltrials.gov.) NCT03641651
Study Identifier:	2018-01214
Sponsor-Investigator and Principal Investigator:	Markus Wirz Zurich University of Applied Sciences (ZHAW) Institute of Physiotherapy Prof. Dr. Markus Wirz Technikumstr. 71 CH 8401 Winterthur Phone: +41 (0)58 934 63 21 Fax: +41 58 935 63 21 E-Mail: markus.wirz@zhaw.ch
Study Intervention:	Technology assisted intensive rehabilitation in subacute stroke
Protocol Version and Date:	Version 02,September the 12th 2018

SIGNATURE PAGE(S)

Study number	2018-01214
Study Title	Feasibility and cost description of intensive rehabilitation involving new technologies in patients with sub-acute stroke: A multicenter single arm trial of the Swiss RehabTech Initiative

Sponsor-Investigator, Principal Investigator and coordinating 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.

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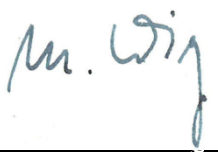


Winterthur, 03.10.2018 _____ _____

Place/Date Signature

Local Principal Investigators at study sites:

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

Site	Rehakliniken Zihlschlacht Hauptstrasse 2-4 8588 Zihlschlacht
Principal investigator	Carsten Möller

Place/Date: Zihlschlacht, 05.10.2018

Signature

Local Principal Investigators at study sites:

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

Site	Reha Rheinfelden Salinenstrasse 98 4310 Rheinfelden
Principal investigator	Frank Behrendt

Rheinfelden, 05.10.2018 

Place/Date Signature

Local Principal Investigators at study sites:

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

Site	Kliniken Valens Rehabilitationszentrum 7317 Valens
Principal investigator	Jan Kool

Valens, 05.10.2018

Place/Date

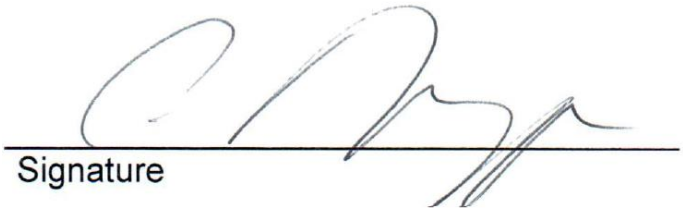
Signature

Local Principal Investigators at study sites:

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

Site	Klinik Lengg AG Bleulerstrasse 60 CH-8008 Zürich
Principal investigator	Christian Sturzenegger

Zürich, 06.10. 2018
Place/ Date



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STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Markus Wirz
Study Title	Feasibility and cost description of intensive rehabilitation involving new technologies in patients with sub-acute stroke: A multicenter single arm trial of the Swiss RehabTech Initiative
Short Title / Study ID	New technologies in the rehabilitation of chronic stroke 2018-01214
Protocol Version and Date	Version 02, September the 12th 2018
Trial registration	clinicalTrials.gov: NCT03641651
Study category and Rationale	Other clinical study Category **A** The phase of development covered by this study pertains to the efficient application of a combination of commercially available rehabilitation technology, corresponding to phase III.
Background and Rationale	Limitations in the performance of activities are a frequent consequence of a cerebro-vascular stroke. Partial paresis, abnormal muscle tone and deteriorated coordination are among others reasons for these deficits. From rehabilitation and motor (re-) learning studies it is known that skilled movements can be trained. The success of such training depends on the context of training, the motivation of the patients and the training intensity. These factors can be tailored and controlled with the use of rehabilitation technologies such as robotics or audio-visual feedback devices. However, up to now only sparse evidence and experience is available on the efficient application of such devices.
Objective(s)	The objective of the current study is to develop and investigate training concepts involving rehabilitation technology, which aim at exploiting the potential for regaining the ability to perform skilled movements by maximizing training intensity while keeping the motivation of patients high. The evaluation focuses on feasibility and cost-benefit analyses.

Outcome(s)	• Variables from the devices such as
	  o number of trainings
	  o training duration, number of repetitions
	  o support
	  o success rate (for game-like tasks)
	• Patient related outcomes
	  o Lower extremities
	  o Upper extremities
	  o Functional independence Measurement (FIM)
	  o Questionnaire for the patients covering:
	  ▪ motivation
	  ▪ adherence
	  ▪ perceived support (Fühlen sie sich gut betreut)
	  ▪ desire to continue such a training
	  ▪ subjective rating of the training modalities (which was the best, which was the most interesting)
	• Adverse events
	  o Medical complications
	  o organizational challenges
	• Economic variables
	  o Descriptives (quantities, prices, operational procedures in the use of the technology)
	  o Efficiency analysis
	  o Reimbursement

Study design	Multicenter-single arm feasibility study
Inclusion / Exclusion criteria	**Inclusion**: • Patients with residual hemiparesis after cerebrovascular accident • Up to 12 months after the event • Primary rehabilitation terminated • Able to cognitively comprehend the aim of the project • General health condition allows for intensive rehabilitative training with limited supervision i.e. clearance of responsible physician • Understand written and spoken German language **Exclusion**: • Presents with contraindication for the training with the respective devices

Study Intervention	• Series of tailored rehabilitative trainings with the use of new technology which provide feedback and allow for a targeted, intensive and dense training. • With limited supervision based on patients preconditions and therapy device (e.g. patient/ therapist ratio= 3/1). • A training series lasts four weeks and comprises 3-5 training-days per week. Maximum training break of 7 days. A minimum of five blocks of training with duration of 45 min per training day each are foreseen. The training can take place in an in- or outpatient setting
Reference Intervention	Not applicable
Number of Participants with Rationale	As this study is a feasibility study: N= 20 (five subjects for every clinical site).
Study Duration	Thirty months (30m) in total.
Study Schedule	11/2018 First-Participant-In (planned) 05/2020 of Last-Participant-Out (planned)
Investigator(s)	Carsten Möller Rehakliniken Zihlschlacht Hauptstrasse 2-4 8588 Zihlschlacht Phone 071 424 33 33 c.moeller@rehaklinik-zihlschlacht.ch Frank Behrendt Reha Rheinfelden Salinenstrasse 98 4310 Rheinfelden Phone 061 / 836 5385 F.Behrendt@reha-rhf.ch Jan Kool Kliniken Valens Rehabilitationszentrum 7317 Valens Phone 081 303 11 11 jan.kool@kliniken-valens.ch Christian Sturzenegger Klinik Lengg AG Bleulerstrasse 60 CH-8008 Zürich Phone 044 387 6901 christian.sturzenegger@kliniklengg.ch
Study Centre(s)	see above

Statistical Considerations	Descriptive analysis Pre-post comparisons of patient–related outcomes
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
PI	Principal Investigator
SAE	Serious Adverse Event
SDV	Source Data Verification
SNCTP	Swiss National Clinical Trial Portal
SOP	Standard Operating Procedure
TMF	Trial Master File

1 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor, Sponsor-Investigator (Principal Investigator)

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1.2 Coordinating Investigator

See Sponsor

1.3 Principal Investigator(s)

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1.4 Statistician (Biometrician)

NA, feasibility study

1.5 Monitoring Institution

Prof. Martin E. Schwab
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Tel. direct +41 44 635 33 30
Secretary +41 44 635 33 31
schwab@hifo.uzh.ch

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

The study will be registered in the Swiss National Clinical Trials Portal (SNCTP) and in the international trial registry ClinicalTrials.gov (clinicaltrials.gov). Registration number: NCT03641651

2.2 Categorization of the Study

Category A: the intervention is clinical standard.

2.3 Competent Ethics Committee (CEC)

The ethical committee of the Canton Zurich is regarded the lead ethical committee. Due to the multicenter status of this trial, the ethical committees of St. Gallen (EK Ostschweiz) and Nordwest-and Zentralschweiz (EKNZ) are also involved and will be asked for approval.

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 conflict of interest by any person involved in conducting this clinical trial.

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.
Such medical information may be given to the participant's personal physician or to other appropriate medical personnel responsible for the participant's welfare, if the patient has given his/her written consent to do so.
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

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

Damage of the neurological system, because of illness or injury, affects over a billion people worldwide [1].This damage can, amongst other consequences, lead to motor impairment, which necessitates rehabilitative treatment. Rehabilitation has been defined by the World Health Organization (WHO) as “active process by which those affected by injury or disease achieve a full recovery or, if a full recovery is not possible, realize their optimal physical, mental and social potential and are integrated into their most appropriate environment” [2]. Literature shows, that intensive training is required to exploit the full potential of recovery. There is in fact overwhelming evidence that more intensive training leads to better rehabilitation outcomes in individuals with stroke [3-14] and reduces hospital readmission rates [15]. However, today, clinical reality looks rather different. Many individuals with motor impairments are discharged from rehabilitation considerably short of attaining their optimal potential. Rather than receiving therapy until their potential is reached, they are discharged when it is considered safe by the third party payers [16]. Actual therapy time during a regular day at a rehabilitation hospital is generally very limited, mostly due to management decisions, lack of structured organization and inefficient use of resources [17, 18]. In four European rehabilitation centers, individuals with stroke received between one and three hours of therapy per day, while over 72% of time was spent with non-therapeutic activities [17]. This has consequences, as these authors also were able to show that patients in centers with less therapy time per day have less functional recovery than those who are treated in centers that provide more therapy time per day [18]. In addition, within a session of conventional therapy, dosage is generally rather low, even during inpatient rehabilitation. For example, Hayward et al. describe that the dose of activity-related arm training only adds up to an average of 4min and as little as 23 repetitions per therapy session during inpatient rehabilitation [19]. Lang et al. found an average number of repetitions per session of 32 for the upper extremity and of 357 for the lower extremity [20].

Individuals post stroke also make significantly less use of their upper extremities throughout the rest of their day during inpatient rehabilitation. While able-bodied control persons use their arms during 8-9hrs per day, individuals with stroke during inpatient rehabilitation use their more affected arm during 3.3 hrs and their less affected arm during 6 hrs per day [21]. This non-use leads to negative plasticity and further impairment [22].

So, while it is certainly possible to intensify therapeutic treatments during inpatient rehabilitation [12, 18], it is challenging for many reasons and often not done. Needless to say that this less than optimal amount of therapy provided results in large amounts of untouched recovery potential. Out of the roughly 15 million people worldwide who experience a stroke each year, 5 million live with permanent disability [1]. The Framingham study for example showed that of all stroke survivors, 20% remain dependent in their mobility [23]. Clearly, this dependency, as well as other under-treated impairments lead to tremendous costs throughout the person’s lifetime [24-27]. For Medicare users in the United States for example, while mean rehabilitation length of stay after an acute stroke was only 14.6 days, readmission rate to the hospital was 12.7% within the first 30 days after discharge from rehabilitation [28]. In Europe, the total cost resulting from strokes was 37.4 billion in 2010 [29]. In Switzerland, in 2014,

25.8% of health costs were spent on acute inpatient treatment, while only 1.7% were spent on inpatient rehabilitation. Outpatient physical therapy only added up to 1.4% of the total health costs [30].
There is a desperate need for affordable solutions to provide our patients the intensity of therapy necessary to optimally exploit their potential for recovery. Finding such a solution must include dialog between all the stakeholders, i.e. patients, clinicians, technological solution providers and insurers. The Swiss Rehab Tech Initiative aims to do exactly that. It provides a platform where all involved parties come together. The initiative is now ready to test a model solution in the clinic.

3.2 Study Intervention and Indication

In a first step, the feasibility of the intervention aims to establish efficient settings in four trailblazer clinics. This will enable them to provide intensive therapy to the patients in accordance with the study protocol. While these settings are integrated into the clinical routine, we will be able to collect data to get some first insight into economic and functional data required to calculate changes in socioeconomic costs.

3.3 Clinical Evidence to Date

Suitable solutions include advanced technology, such as electromechanically assisted gait and arm trainers, which is one way to allow reaching high training intensities [31, 32]. These devices take the physical burden from the therapists, thus allowing training duration to be limited by the patient's capabilities rather than by exhaustion of the therapists. With the assistance of such devices, participants in one study performed up to over 600 functional arm movements per session [33]. Another study describes walking distances of up to 2000m (roughly 3300 steps) per session in an individual with spinal cord injury [34]. Technology assisted training has received considerable attention over the past years. This is reflected in a large number of published research studies. Numerous individual trials and several systematic reviews [35-38] have shown the positive effects of robotic assisted gait training, as well as of technology assisted training of the upper extremity [35, 36, 38, 39]. Cochrane Reviews showed that every fifth gait dependency could be prevented if patients received electromechanically assisted gait training in addition to their regular therapy program [40] and that electromechanical and robot-assisted arm training leads to improvements in activities of daily living and arm function [41] in individuals post stroke. Similar to physical therapy in general, it was also shown for technology assisted gait training that more intensive training programs lead to improved outcomes [42].
All these studies have shown that it is in fact possible to improve outcomes through intensifying training paradigms.

3.4 Justification of Study Intervention

Treatment intensification so far has often taken place within a research environment and with the corresponding reimbursement through grants or other sources. In order to show the effect under clinical every day conditions and reimbursement situations, efficient settings have to be integrated into rehabilitation institutes and their effect on

patient outcome as well as economic parameters have to be shown. Investing into new technologies to provide efficient settings and delivering high intensive therapy as requested by clinical evidence is currently the sole responsibility of healthcare providers. It is not reimbursed either through support of investments or reimbursement. Specifically with certain reimbursement models, such as diagnosis related groups, there is no incentive for rehabilitation institutions to invest in such therapy models and provide more therapy for their patients.

3.5 Explanation for Choice of Comparator Intervention

Not applicable, pilot study without control intervention

3.6 Risk / Benefits

As the technological devices under study have already been certified as medical devices and are currently used in involved clinics, there are no adverse risks to be expected. To examine the benefits of this intervention by using specific outcome measurements is part of this research project. Further aspects are discussed under point 4.4 (Safety outcomes).

3.7 Study Population

The study aims to target on patients with a residual hemiparesis after a cerebrovascular accident up to 12 month ago. The primary rehabilitation has terminated. Their general health conditions should be stable to allow nearly daily intensive rehabilitation. Patients should cognitively and educationally be able to communicate verbal and non-verbal in German language. Specific inclusion and exclusion criteria are specified under 7.1. Each involved clinical site aims to include five patients. The enrolment procedure will be iterative with one or two clinics starting the recruitment. A total of twenty (n=20) patients are aimed to be enrolled.

4 STUDY OBJECTIVES

4.1 Overall Objective

This feasibility project aims to establish an efficient setting for intensive rehabilitation with new technology in four trailblazer clinics. This will enable them to provide intensive therapy to the patients in accordance with the study protocol. If this setting is integrated into the clinical routine, we will be able to collect data to get some first insight into economic and functional data required to calculate changes in socioeconomic costs.

4.2 Primary Objective

Develop and investigate the feasibility of a rehabilitative training program adopting new technologies, which focuses on scientifically based intensity and efficiency.

4.3 Secondary Objectives

Describe economic costs of the program.
Document and evaluate functional changes in response to the training.

4.4 Safety Objectives

All medical devices will be used as indicated. Involved physiotherapists will be trained in using the devices and supervising the training. Every clinic has its emergency plan, which will be applied in case of need
Participants will be supervised permanently during the intervention. No adverse events (AE) or serious adverse events (SAE) are expected to occur. However, participating subjects might complain about tiredness or muscle soreness due to the intensive intervention, which will be recorded on the case report form (CRF).
All adverse (AE) and serious adverse events which will be defined later (Point 10) whether related or unrelated will be recorded in the case report form (CRF). The CEC will be informed of any SAE within 15 days.

4.5 Primary Outcome

The primary outcome is to assess the feasibility of planned trainings. Every training and training day will be described in terms of

- devices used,
- duration of training,
- training mode (passive, active or resistive) and
- feedback given by the device.

The specific interest is the adherence of the patients:

- to planned trainings in terms of planned vs. actually performed training-days and training intensity.

- the subjectively perceived effort by the patients to perform the trainings will be recorded on a visual analogue scale (VAS).
- the subjectively perceived effectiveness will be recorded by using the “Patients Global Impression of Change” = PGICS)

4.6 Secondary Outcomes

Secondary outcomes are patient-related outcomes:

- generic functional and specific functional performance, focusing on upper and/or lower extremity and measured by rater observing patients during standardized tests. The tests used will be listed later at point 9.2 by the “Functional independence measurement” (FIM)
- specific functional assessments of the upper AND/OR lower extremity
    - Stroke impact scale (SIS)
- upper extremity:
    - Fugl-Meyer test
    - Box and Block test
- lower extremity:
    - Functional ambulation categories (FAC)
    - Comfortable walking speed (10m Walk test= TMT)
    - Chedoke-McMaster Stroke Assessment Measure (CMSA), the walking index
    - Berg Balance scale (BBS)
- health-related quality of life (EQ-5D)

- **Cost elements** and structures for cost description analysis
    - quantities and prices of inputs (staff, technologies, infrastructure)
    - intensity of use of new rehabilitation technologies
    - h/day, h/week, time of the day
    - description of operational procedures
    - patient(device)/therapist ratio
    - identification of main drivers for increasing efficiency
    - efficiency gains
    - current reimbursement
    - future reimbursement possibilities and models

4.7 Safety Outcomes

Participating patients will be monitored constantly by attending physiotherapists. The ratio of patient to therapist will be between 1:1 and 3:1. Physiotherapists are specially trained in the use of the devices and in life saving measures. Only patients regarded “stable” by their physician to conduct the program will be included.
The subjectively perceived effort by the patient and during the training will be noted on the CRF. Heart rate frequency and blood pressure can be monitored if necessary.

5 STUDY DESIGN AND COURSE OF STUDY

5.1 General Study Design and Justification of the Design

Since the aim of this feasibility study is the development and validation of a new treatment program and not yet, the investigation of effectiveness while controlled with a current state of the art intervention, no control group will be included. A longitudinal single group design has been chosen. Blinding of therapists and patients is accordingly not possible. Blinding of assessment cannot be guaranteed, due to logistical reasons and as assessments are either self-conducted or by attending therapists, who are trained in doing so.

5.2 Study Duration and Study Schedule

The duration of this study is planned to be 30 months (i.e. 2.5 years). The completion depends on the rate of recruitment.

Clinics start recruitment at different dates.

Clinic	**Start of recruitment**
Klinik Lengg	01.11.208
Reha Rheinfelden	01.11.2018
Kliniken Valens	01.11.2018
Rehaklinik Zihlschlacht	01.11.2018

Project and study schedule

		Project months															
WP		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
1 Set-up of infrastructure and processes																		
2 Patient trainings/-assessments																		
3 Analysis/ Dissemination																		
4 Communication																		
5 Project management																		
Milestones	Funding acquired	◆																
	KEK Approval				◆													
	First patient, first visit					◆												
	Interim Analysis											◆						
	Last patient, last visit														◆			
	Final Analysis																	◆

5.3 Methods of Minimizing Bias

Not applicable as no control intervention will be conducted, no randomization and/or blinding for the study design can be applied. Clinics will undertake measures to minimize tester bias.

6 STUDY POPULATION

Four rehabilitation centres located across the German speaking area of Switzerland will participate in this project.

Klinik Lengg, Zurich
The Klinik Lengg has a workload of 250-stroke patients a year. All patients fulfilling the inclusion criteria will be asked for participation.

Reha Rheinfelden
The Reha Rheinfelden has a workload of approximately 400 ischaemic and haemorrhagic stroke patients as in-and outpatients a year, which will recruited via direct contact, clinic's database, and flyer distributed in-house.

Kliniken Valens
Kliniken Valens treated approximately 460 ischaemic and 150 haemorrhagic stroke in-patients a year, who will be approached by a research assistant to check their eligibility while entering the clinical site for inpatient rehabilitation.

Rehaklinik Zihlschlacht
The Rehaklinik Zihlschlacht has a yearly workload of approximately 300 stroke patients; some of them will be treated after discharge in the clinic's outpatient setting. Study personnel will approach patients regarded eligible for further evaluation.

Each site aims to include five patients leading to 20 patients in total. Study sites are entering the study consecutively and according to their personnel capacity.

6.1 Eligibility Criteria

6.1.1 Inclusion Criteria

Patients fulfilling all of the following inclusion criteria can be enrolled in the study

- Adult patients with residual hemiparesis after cerebrovascular accident
- Up to 12 months after the event
- Primary rehabilitation terminated
- Able to cognitively comprehend the aim of the project
    - At least 22 points in the Montreal Cognitive Assessment (MoCA)
- General health condition allows for intensive rehabilitative training with limited supervision i.e. clearance and prescription of responsible physician
- Understand written and spoken German language

6.1.2 Exclusion Criteria

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

- Patients with any signs and symptoms showing that the participant is unwilling to participate in the study will result in the patient being excluded from participation
- Any medical condition preventing participation such as

- Severe respiratory disease
- Severe OR unstable cardio-circulatory conditions
- Orthopaedic conditions, especially in extremities targeted for rehabilitation such as
  - fixed joint contractures limiting range of motion
  - non-consolidated fractures
- Neuro-psychological conditions including cognitive deficits limiting communication or non-cooperation like (self-) aggressive behaviour
- Infections or inflammatory diseases, like osteomyelitis

- Specific **absolute contraindication** for the training **with any of the respective** devices:
  - Improper fit of the device, including its harness to relevant extremity(ies)
  - Contraindicated training position (standing, sitting)

Device specific contraindications will be respected and will lead to the exclusion of the device for that patient.

The choice of the device is dependent by the patient's goal, primary impaired limb, and availability at the study site. Comparison of devices is not intended, but to measure the feasibility of their intensive use.

Devices from Hocoma AG Switzerland HocomaProducts
- Lokomat
- Erigo
- Andago
- Armeo (Boom, Senseo, Spring, Power)
- Valedo Motion

Devices from Tyromotion Austria Tyromotion
- Amadeo
- Myro

Devices from other manufacturers
- Devices from NuStep: NuStep
- The Bi-Manu-Trainer by Reha Stim: Bi-Manu-Trainer
- The EksoGT by EkSo Bionics, USA: Ekso GT
- The Float by Lutz Medical Engineering, Switzerland: The Float
- Devices from Reck MOTOmed: MOTOmed
- Allegro Medical device by Dynamic devices: Dynamic Devices

Physicians, not participating in the study, safeguard patient interest and insures proper medical care at every clinical site.

6.2 Recruitment and Screening

Eligible in-and or outpatients attending at each clinic and fulfilling the inclusion criteria will be screened by trained medical personal at each site.
The screening procedure of each participating clinic has been described before (point 6.1).

6.3 Assignment to Study Groups

NA, every patient will be assigned to the intervention under study.

6.4 Criteria for Withdrawal/ Discontinuation of Participants

Patients not willing to adhere to the protocol will not be included. For included patients who, while having already attended some session but are not able to complete the six weeks program within the intensity planned, a tailored reduction of intensity in terms of days, hours per days and/or sessions per day is considered. A maximum training break of 7 days is foreseen
Patients who withdraw before the start of the study will be replaced.

7 STUDY INTERVENTION

7.1 General Information

7.1.1 Study Intervention

- Series of tailored rehabilitative training with the use of new technology which provide feedback and allow for a targeted and intensive and dense training.
- With supervision based on patients preconditions and therapy device (e.g. patient/ therapist ratio= 3/1).
- A training series lasts four weeks and comprises 3-5 training-days per week. Maximum training break of 7 days. Five sessions of training with duration of 45 min per session, and up to four hours each day are foreseen.
- The training can take place in an outpatient or inpatient setting.
- Training will be organized in individual one-to-one or group sessions.

7.2 Administration of Study Intervention

7.2.1 Study Intervention

Interventions will be applied and supervised according to the needs, aims and planned interventions (devices used) for each patient individually. Adaptations to a minimum program as outlined under 6.4. can be made.

7.2.2 Control Intervention

n.a.

7.3 Compliance with Intervention

For every patient a CRF including a trainings and intervention plan will be completed. This plan includes measurements to adherence to the intervention plan. The trainings plan will be made in advance and in collaboration by both patient and therapist, including all scheduled days and sessions (devices). Patients not able or willing to fulfil the minimum program outlined before (6.4) will be excluded.

7.4 Data Collection and Follow-up for Withdrawn Participants

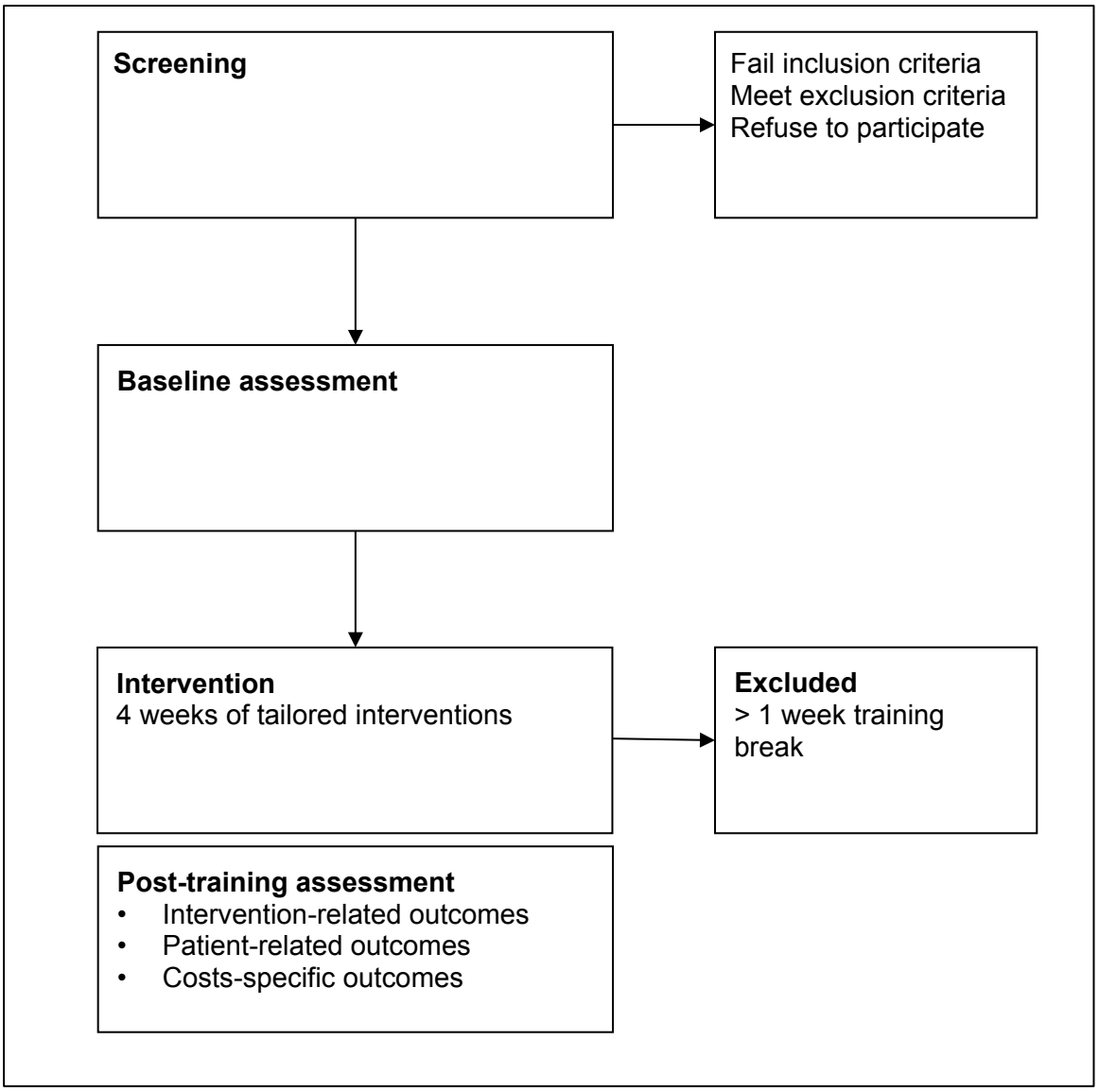
Data of all included patients will be analyzed. A follow-up is not planned.

7.5 Concomitant Intervention(s)

All co-interventions such as medication used or other therapies visited during the trial will be recorded.
All concomitant and/or rescue interventions or treatment(s) will be recorded in the *CRF.*

8 STUDY PROCEDURES

8.1 Study Flow Diagram



8.2 Assessments of Outcomes

8.2.1 Assessment of Primary Outcome (daily)

The primary outcome is to assess the feasibility of planned trainings. Every training and training day will be described in terms of

- device used,
- duration of training
- training mode (passive, active or resistive)
- feedback given

The specific interest is the adherence of the patients

- to planned trainings in terms of planned vs. actually performed training-days and training intensity.
- The subjectively perceived effort by the patients to perform the trainings will be recorded on a visual analogue scale (VAS).
- The subjectively perceived effectiveness will be recorded by using the “Patients Global Impression of Change” = PGICS)

The primary outcomes will be assessed at each intervention day. Either during the training, at the end of each training or at the end of each training day. The PCICS will be assessed at the end of the whole intervention.

8.2.2 Assessment of Secondary Outcomes (Baseline and end of study)

Secondary outcomes are patient-related outcomes are:

- generic functional performance measured by the “Functional independence measurement” (FIM)
- specific functional assessments of the upper AND/OR lower extremity
- Stroke impact scale (SIS)
- Upper extremity:
    - Fugl-Meyer test
    - Box and Block test
- Lower extremity:
    - Functional ambulation categories (FAC)
    - Comfortable walking speed (10m Walk test= TMT)
    - Chedoke-McMaster Stroke Assessment Measure (CMSA), the walking index
    - Berg Balance scale (BBS)
- Health-related quality of life (EQ-5D)

Patient-related outcomes will be assessed after the last training session. These outcomes will be assessed at baseline and at the end of the intervention by raters observing the patient during aforementioned tests. During final assessment, raters will be kept blind to the baseline values.

Cost elements and structures for cost description analysis

- quantities and prices of inputs (staff, technologies, infrastructure)
- intensity of use of new rehabilitation technologies
    - h/day, h/week, time of the day
- description of operational procedures

    - patient(device)/therapist ratio
- identification of main drivers for increasing efficiency
- efficiency gains
- current reimbursement
    - future reimbursement possibilities and models

Secondary outcomes will be assessed at baseline and at the end of the intervention by raters observing the patient during aforementioned tests. During final assessment, raters will be kept blind to the baseline values.

8.2.3 Assessment of Safety Outcomes

8.2.3.1 Serious Adverse Events

Recording of serious adverse event (SAE) information, what information needs to be collected: time of onset, duration, resolution, action to be taken, assessment of intensity, relationship with study treatment; refer to Section 9 for SAE definition and procedures; define specific process to ask the participant at the visits about adverse events, collection of spontaneous reports.

8.2.3.2 Laboratory Parameters

NA

8.2.3.3 Vital Signs

Patient self-perceived effort during each training session as expressed by a VAS will be recorded.

8.2.4 Assessments in Participants who prematurely Stop the Study

Project investigators at each site will contact patient who withdrew from the study. Patients will be asked for reasons of withdrawal

8.3 Procedures at each training day

At each training day, the participant and responsible physiotherapist will plan the program of the day according to the **training plan (CRF page 53)**. During each training bloc a physiotherapist will supervise the patient. Intervention-related outcomes will be completed after or during each training bloc and at the end of each training day.

8.3.1 Screening Visit

During the screening procedure, eligibility criteria will be checked by study personnel at each clinic and informed consent will be obtained.

8.3.2 Baseline Visit

During the initial visit, **patient related outcomes** will be obtained.
For every patient a trainings- and intervention plan (CRF page 53ff) will be established.

8.3.3 Start of training

In the beginning of each training day, patient and therapist will plan the day including sessions, and devices to be used.

8.3.4 End of study

After the intervention will end, and patient-related outcomes will be obtained either by self-report or measured by an observer.

9 SAFETY

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.

9.1 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.

9.2 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.

9.3 Reporting of Serious Adverse Events

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 sponsor **within 24 hours** after they become known; and
- to the CEC **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 CEC of these measures, and of the circumstances necessitating them, **within 7 days**.

Annual Safety Report

All SAEs will be summed up in the **annual safety report (ASR)** and submitted to the CEC. 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).

9.4 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 return for a follow-up investigation. This visit will take place up to 30 days after terminating the treatment period. Follow-up information on the outcome will be recorded on the respective SAE page in the CRF.
Follow-up investigations may also be necessary according to the investigator's medical judgment even if the participant has no SAE at the end of the study. However, information related to these investigations does not have to be documented in the *CRF* but must be noted in the source documents.

10 STATISTICAL METHODS

10.1 Hypothesis

Not applicable, as this study is a feasibility study. **Determination of Sample Size**

Twenty patients, five at each site are planned to be enrolled. A sample size calculation is not applicable for this feasibility study.

10.3 Planned Analyses

The analysis of **intervention-related outcomes** is primarily regarded descriptive. For **patient-related outcomes** parametrical and/or non-parametrical univariate statistics for pre-to post changes will be used.

10.3.1 Primary Analysis

Intervention-related outcomes: Absolute and relative frequency together with parameters of central tendency and spread will be derived for any devices used, duration of intervention per day, per session, per device. This applies analogously for training and feedback modes used and for self-perceived exertion rates. Adherence rates will examined by using Chi-Square statistics.

10.3.2 Secondary Analyses

For **patient related outcomes** pre-post analysis will be performed by parametrical or non-parametrical univariate tests. Subgroup analysis for upper and or lower extremity will be done.

For Cost elements and cost description analysis, descriptive analysis will be performed including costs for technology, staff and infrastructure. Efficiency gains and suitable reimbursement models will be calculated.

10.3.3 Interim Analyses

n.a.

10.3.4 Safety Analysis

n.a.

10.3.5 Deviation(s) from the Original Statistical Plan

n.a.

10.4 Handling of Missing Data and Drop-Outs

Primary analysis is according to intention to treat – and all patients will be included.

For secondary analysis, all participants with equal or less than seven days training break of the planned training will be included only.

Analysis of drop-outs will be carried out to find reasons or barriers (CRF) that might explain why sticking to the treatment plan was not possible, whether related or unrelated to the intervention.

11 ELIGIBILITY OF THE PROJECT SITE(S)

Four rehabilitation centres located across the German speaking area of Switzerland will participate in this project.

Klinik Lengg, Zurich
The Klinik Lengg has a workload of 250-stroke patients a year. All patients fulfilling the inclusion criteria will be asked for participation.

Reha Rheinfelden
The Reha Rheinfelden has a workload of approximately 400 ischaemic and haemorrhagic stroke patients as in-and outpatients a year, which will recruited via direct contact and flyer distributed in-house.

Kliniken Valens
Kliniken Valens treated approximately 460 ischaemic and 150 haemorrhagic stroke in-patients a year, who will be approached by a research assistant to check their eligibility while entering the clinical site for inpatient rehabilitation.

Rehaklinik Zihlschlacht
The Rehaklinik Zihlschlacht has a yearly workload of approximately 300 stroke patients; some of them will be treated after discharge in the clinic's outpatient setting. Study personnel will approach patients regarded eligible for further evaluation.

Each site aims to include five patients leading to 20 patients in total. Study sites are entering the study consecutively and according to their personnel capacity. **Each site aims to include five patients** leading to 20 patients in total. Study sites are entering the study consecutively and according to their personnel capacity.

12 DATA QUALITY ASSURANCE AND CONTROL

The Sponsor-Investigator will provide all study sites with case report forms and written instructions. All study sites ensure that the trial is 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.

12.1 DATA HANDLING AND RECORD KEEPING

The study will strictly follow the protocol. If any changes become necessary, they must be laid down in an amendment to the protocol. All amendments of the protocol must be signed by the Sponsor-Investigator and if essential submitted to CEC.

12.1.1 Case Report Forms

The investigators will use *paper* case report forms (*CRF*), one for each enrolled study participant, to be filled in with all relevant data pertaining to the participant during the study. All participants who either entered the study or were considered not eligible or were eligible but not enrolled into the study additionally have to be documented on a screening log. The investigator will document the participation of each study participant on the Enrolment Log.
CRFs will be kept current to reflect participant status at each phase during the course of study. Participants must not to be identified in the *CRF* by name. Appropriate coded identification (e.g. **SRTI_ClinicCode_Number)** must be used.
It must be assured that any authorized person, who may perform data entries and changes in the *CRF*, can be identified. A list with signatures and initials of all authorized persons will be filed in the study site file and the trial master file, respectively.
The investigators assure to perform a complete and accurate documentation of the participant data in the *CRF*. All data entered into the *CRF from original questionnaires and assessment sheets will* also be available in the individual participant file either as print-outs or as notes taken by either the investigator or another responsible person assigned by the investigator.
Essential documents will be retained for at least 10 years after the regular end or a premature termination of the respective study (KlinV Art. 45).
Any patient files and source data will be archived for the 10 years at each study site.

12.1.2 Specification of Source Documents

The following documents are considered source data, including but not limited to:

- SAE worksheets
- Case report forms

Source data must be available at the site to document the existence of the study participants and substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant.

The following information (at least but not limited to) should be included in the source documents

- Demographic data (age, sex)
- Inclusion and Exclusion Criteria details
- Participation in study and signed and dated Informed Consent Forms
- Visit dates
- SAEs (related) and concomitant medication
- Reason for premature discontinuation

12.1.3 Record Keeping / Archiving

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial at each study site in a lockable and fireproof place. Informed consents and CRFs will be archived in separate places. Original study documents including any documents with personal information will be kept at the study site. There will be kept in fireproofed locker, accessible only by Study personnel. Copies of CRFs, including the clinic code will be transferred to the Sponsor investigator site and will be kept on a secure data pool only accessible by involved study personnel. The data pool will be closed after the end of the study and will by then only be accessible according to the separation of duties (SOD) principle.

12.2 Data Management

Copies of the CRF will be transferred by each site investigator and uploaded on a security pool at the sponsor investigators site. Original data will be kept at the clinical site in a lockable and fireproof place, the informed consent will be separated from other documents. Only study personnel involved in the clinical trial will have access to that security pool. No personnel data will be transferred but kept at each study site and separated from the CRF. Data from CRFs will be entered to electronic spreadsheets using double data entry and saved as raw file. During further data processing and analysis, edited files will be renamed with actual dates and acronyms of the responsible person. Original files (paper or electronic) will not be changed

12.3 Routine Monitoring

Monitoring visits at the investigator's site prior to the start and during the course of the study will help to follow up the progress of the clinical study, to assure utmost accuracy of the data and to detect possible errors at an early time point. The Sponsor-Investigator organizes professional independent monitoring for the study.
All original data including all patient files, progress notes and copies of laboratory and medical test results must be available for monitoring. The monitor will review all or a part of the *CRF* and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents.

12.4 Audits and Inspections

A quality assurance audit/inspection of this study may be conducted by the CEC. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study.
The investigator will allow the persons being responsible for the audit or the inspection to have access to the source data/documents and to answer any questions arising. All involved parties will keep the patient data strictly confidential.

12.5 Confidentiality, Data Protection

Direct access to source documents will be permitted for purposes of monitoring, audits and inspections to the authorities of the responsible ethical committees.

13 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.

14 FUNDING AND SUPPORT

14.1 Funding

This study receives funding from an anonymous Swiss Foundation.

14.2 Other Support

NA

15 INSURANCE

Insurance is covered by “Versicherung für klinische Versuche und nichtklinische Versuche“ by Zürich Versicherungs-Gesellschaft AG (Policy no.: 14.237.322).
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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