Validation of a digital twin to predict the adaptation of muscle strength and muscle size due to strength training.

Research legislation:	Ordinance on human research with the exception of Clinical trials (HRO) [1].
Type of Research Project:	Research project involving human subjects (other clinical trial)
Risk Categorisation:	Risk category A according to Art. 61 KlinV
Project Leader:	Prof. Dr. Silvio Lorenzetti ZHAW Leiter Fachabteilung MPS Technikumstrasse 9 CH-8400 Winterthur silvio.lorenzetti@zhaw.ch

PROTOCOL SIGNATURE FORM

Study Title	Validation of a digital twin to predict the adaptation of muscle strength and muscle size due to strength training.

The project leader has approved the protocol version ***[v7,18.07.2024]***, and confirms hereby to conduct the project according to the protocol, the Swiss legal requirements [1, 2], current version of the World Medical Association Declaration of Helsinki [3] and the principles and procedures for integrity in scientific research involving human beings.

Project leader:

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GLOSSARY OF ABBREVATIONS

BASEC	*Business Administration System for Ethical Committees*
CSA	*Cross Sectional Area*
CRF	*Case Report Form*
EMG	*Electromyography*
FOPH	*Federal Office of Public Health*
H:Q Ratio	*Ratio between Hamstrings and Quadriceps strength*
HMF	*Host Mesh Fitting*
HRA	*Human Research Act*
HRO	*Ordinance on Human*
IMU	*Inertial Measurement Unit*
iPhone	*Mobile Phone by Apple Inc.*
iOS	*Mobile Operating System by Apple Inc.*
ISAK	*International Society for the Advancement of Kinanthropometry*
PI	*Principal Investigator*
1RM	*One Repetition Maximum*
SCMI	*Swiss Centre for Musculoskeletal Imaging*
(S)AE	*(Serious) Adverse Event*
ZHAW	*Zürcher Hochschule für angewandte Wissenschaft*
SNCTP	*Swiss National Clinical Trials Portal*
watchOS	*Operating System for the Apple Watch*
BASEC	*Business Administration System for Ethical Committees*

1 BACKGROUND AND PROJECT RATIONALE

Musculoskeletal diseases and pain are a major concern and financial burden for the Western society due to the progressively aging population, and an increasing percentage of people working in a seated position [4, 5]. Additionally, the incidences of acute injuries to the musculoskeletal system remain the most frequently reported occupational injuries in the healthy population, with often long-term consequences for patients and associated medical costs [6].

1.1. Fitness and strength training

Muscular strength training interventions have long been a cornerstone in the prevention, non-surgical management and rehabilitation of the entire spectrum of musculoskeletal injuries and diseases in athletes, healthy adults, patients and the elderly [7-9]. Strength training has been shown to enhance general fitness and the deposition of bone mass in healthy adults [9], improve activity levels and independence of senior adults [10], enhance the performance of competitive athletes [11], as well as help in the prevention and rehabilitation of musculoskeletal injury and disease [8]. Furthermore, a recent large-scale epidemiological study in over 80,000 adults suggested a 31% reduction of cancer mortality in subjects that adhered to strength training over and above the generic physical activity targets [7].

The key goal of muscular strength training is to regain, maintain or enhance musculoskeletal function. Yet, despite the widespread use of muscular strength training across sports and health care practice, there remains a fundamental lack of understanding with regards to the relationship between subject-specific anatomy, musculoskeletal function and different strength exercises to ensure training safety and efficiency because of limitations in assessing these parameters outside the research setting. Consequently, fitness instructors, coaches, physiotherapists and clinicians continue making training recommendations based on subjective and generalised guidelines, with possibly ineffective or sometimes harmful consequences for individual patients and athletes.

1.2. Computational musculoskeletal models

Computational models of the musculoskeletal system have played a key role in sports and clinical biomechanics to help understand how different types of strength exercises and execution forms are affecting musculoskeletal function [12]. Computational models of the musculoskeletal system in combination with data from marker-based optical motion capture, ground reaction forces and/or Electromyography (EMG) have been applied to strength training to analyse the best choice and execution form to avoid injury [13-18]; the internal loading state of differently sized people using the same exercise machines [19]; as well as changes in musculoskeletal loading for different exercises and execution forms [18].

Yet, one key challenge that remains to be addressed is the capturing of subject-specific anatomical differences. Numerical techniques to fit so-called generic models to subject-specific anatomical data have remained computationally very involved and too time-consuming for wide-spread application outside the research setting. It remains commonly assumed in sports science that a limited number of body surface trajectories (e.g. bony anatomical landmarks) sufficiently reflect the subject-specific anatomy of the entire musculoskeletal system; which is problematic especially when investigating muscular imbalances, postural alignment and musculoskeletal limitations or gains due to strength training interventions.

In preliminary research, post-doctoral scientist Dr. Oberhofer has assessed the feasibility of fitting generic musculoskeletal models to a limited number of subject-specific body surface data using a free-form deformation technique called Host Mesh Fitting (HMF) [20-22]. The HMF technique is a geometric free-form deformation technique for fitting generic anatomically-based musculoskeletal models to a limited number of 3D body surface data. The HMF objective function is set up to find the optimum mesh nodal parameters that minimise the Euclidean distances between the subject-specific data points and their projections onto the surface mesh of the generic musculoskeletal model in a least-square sense. The position and deformation of the embedded soft-tissue muscle-tendon structures are derived from the deformation of the skin

mesh. The HMF technique was initially introduced to develop high-order finite element models of individual organs, and later applied and validated for predicting the deformation of muscle-tendon structures in the lower limbs during walking [20].

In the scope of a validation study using data from Magnetic Resonance Imaging (MRI) as gold standard, a generic anatomically-based model was fitted to subject-specific data of six children with cerebral palsy and five children without cerebral palsy. The HMF led to better predictions of muscle volumes and lengths than conventional scaling, with the average error between MRI and HMF being less than 10% for muscle lengths and less than 30% for muscle volume [22]. Further improvements are expected by considering individual body composition (i.e. somatotype) and developing a library of musculoskeletal models for different body shapes and population groups.

1.3. Mobile monitoring technology

Mobile monitoring technology, including Inertial Measurement Units (IMU) and optical image capture technology, are becoming readily accessible in ubiquitous devices such as smartphones and smartwatches [23-27] and have become a global research topic to monitor strength training progress. However, while some investigations on commercially-available mobile technology exist to detect exercise type and repetition count, there is still a lack of scientifically-based research to reveal insights into exercise safety and efficiency based on biomechanical principles [28]. Furthermore, the assessment of execution diversity between strength exercises and individual subjects continues to be a key challenge [27]. In comparison to endurance activities, such as outdoor running, the intensity estimation and execution diversity of strength training workouts requires more advanced numerical analysis of the available data [25].

The PI and his research group have started analysing the validity and reliability of commercially available devices in combination with an in-house developed, numerical algorithm for the mobile operating system by Apple Inc. (iOS) to assess musculoskeletal function during strength training outside the research or clinical setting. In particular, an advanced iOS motion-recognition application, named *iOS Strength Control app,* was developed using data from the Apple Watch to identify the type of exercise, repetition count and One Repetition Maximum (1RM) [29-34]. Thereby, research has clearly shown that the quantification of 1RM, as the maximum load that can be lifted through a full range of motion, is fundamentally important when it comes to the design of safe and efficient resistance training programs [31, 35, 36].

The validity, reliability and accuracy of the *iOS Strength Control app* was assessed outside the laboratory setting in 30 physically healthy subjects, all participating in their own weight training program 1-4 days per week, and for three barbell exercises (i.e. deadlift, bench press, back squat) [33]. Excellent accuracy was demonstrated in exercise recognition and repetition count; yet further development and validation are required to improve the accuracy and reliability in the assessment of exercise execution (joint motion and velocity) and 1RM. Here, previous research has shown that the accuracy in the calculation of 1RM depends on the velocity and joint range of motion during exercise execution, which require more advanced numerical algorithms in biomechanics to be derived.

1.4. Project rationale

The rationale of this 4-year project which started at the Swiss Federal Institute of Sport Magglingen (SFISM) and continues at the Zürcher Hochschule für angewandte Wissenschaften (ZHAW) is to apply and validate novel approaches in subject-specific anatomically-based modelling and mobile monitoring to an intervention study in healthy volunteers to predict adaptation in muscle strength and muscle size due to different strength training volume. Individual strength training guidelines, and monitoring of adherence to exercise guidelines for ensuring training safety and efficiency, remain difficult because of limitations in assessing subject-specific anatomical and functional parameters in the training-specific setting. As a consequence, strength training continues to be largely based on subjective expertise, with possibly ineffective or even harmful consequences for individual athletes and patients.

In the scope of this study, we will conduct an 8-week strength training intervention study of key muscle-tendon groups associated with knee joint stability in three study groups with different levels of training volume, with the goal to predict changes in muscle strength and muscle size in relation to training-specific parameters based on subject-specific musculoskeletal modelling and mobile monitoring. Based on subject-specific data MRI in a sub-group of participants, we will further be able to refine validate the HMF technique with the highest accuracy possible.

The outcome will provide new insights into the relationship between subject-specific anatomy, musculoskeletal function and strength training design, which will advance current knowledge in sports science and help to inform strength training recommendations for individual athletes and patients. Technically, we will be able to answer the key research question 'How accurately can changes in muscle strength and muscle size be predicted based on training volume using the novel computational and mobile monitoring technologies?'. The insights and technological advances gained from this study will provide novel means for coaches, clinicians and physiotherapists to answer key questions, such as 'Which strength and rehabilitation training design is best suited for an individual subject to maximise training benefits?'. Thereby, the application of research outcomes will not only benefit athletes but there is tremendous potential also in advancing community-based initiatives and public health services by informing and supporting safe and effective strength training practice.

1.5. Risk category

A (HRO art. 7). This project complies with the definition provided: „Ein Forschungsprojekt entspricht der Kategorie A, wenn die vorgesehenen Massnahmen zur Entnahme von biologischem Material oder zur Erhebung von Personendaten nur mit minimalen Risiken und Belastungen verbunden sind." The overall risk for participants is minimal, with the risk of harm due to the procedure itself being minimized by the design of the protocol.

All the methods and techniques that are used for data collection are non-invasive and hold minimal risks for participants. The strength exercises as part of the intervention study are identical with the exercises that are being performed in usual fitness and rehabilitation routines. Measurement methods include anthropometric measurements, 3D body surface scanning, ultrasound, isokinetic tests, optical motion capture, IMU measurements via the watchOS and a health- & training-related questionnaire; as well as MRI of the lower limbs in a sub-group of participants.

3D body surface data will be obtained using a structured light body surface scanner at the ZHAW, taking only a few seconds with extremely high accuracy between the scanned and the actual body volume without requiring any physical contact [37]. Anthropometric data will be acquired according to general athlete sports practice in line with recommended standards of the International Society for the Advancement of Kinanthropometry (ISAK). Ultrasound and isokinetic strength tests will be done according to established protocols at the Swiss Olympic Medical Centre but executed at the ZHAW. IMU measurements and optical motion capture require small reflective markers or sensors to be attached to the body surface. Possible skin irritations are very rare and can be locally treated (creams). MRI is the gold standard technique for musculoskeletal imaging without exposing the subject to harmful radiation [38]. In case a person feels uncomfortable inside the MRI tunnel due to claustrophobia or other reasons, the imaging can be discontinued anytime. The same holds for isokinetic tests, ultrasound, 3D body surface scanning and marker-based optical motion capture, should a participant feel uncomfortable or exhausted.

The study design and image parameters are all defined according to previous research by Dr. Lorenzetti and his research team at the ETH Zurich, the SFISM and the ZHAW [15, 16, 18, 22, 31, 33, 38-43]. Thereby, the Swiss Olympic Medical Center employs a specialised and praxis-oriented team of clinical experts in sports physiotherapy and functional testing of muscular strength and core competencies with state-of-the-art imaging of the musculoskeletal system.

Dynamic COVID-19 guidelines and strict safety and hygiene measures are in place at the ZHAW to ensure minimum risks for participants with regards to the ongoing pandemic.

2 PROJECT OBJECTIVES AND DESIGN

2.1 Hypothesis and primary objective

Hypothesis: It is hypothesized that advanced subject-specific musculoskeletal modelling in combination with mobile monitoring technology as embedded in the iPhone and Apple Watch allow for accurate prediction of changes in muscle strength and muscle size in the lower limbs following an 8-week strength training intervention of key muscle-tendon groups associated with knee joint stability.

Primary Objective: Prediction of changes in muscle strength in the lower limbs due to different strength training volumes by means of the advanced computational modelling, biomechanical analysis and mobile monitoring technology. Of particular interest is the prediction of 1RM and the prediction of the ratio between hamstrings and quadriceps strength (H:Q ratio) compared against isokinetic strength tests as gold standard. Research has clearly shown that the quantification of 1RM is fundamentally important when it comes to the design of safe and efficient resistance training programs. Improved accuracy in the 1RM prediction compared to preliminary studies (i.e. mean %error of 0.27% in 60% and 7.81% in 80% 1RM assessment [29-34]) is expected through the consideration of data from optical motion capture as well as the additional consideration of subject-specific musculoskeletal anatomy from computational modelling.

Secondary Objective: Assessment of changes in muscle size in the lower limbs due to different strength training volumes using the HMF technique. Of particular interest is the prediction of muscle volume using the HMF technique compared against data from MRI as gold standard, as well as the prediction of adaptation in hamstrings and quadriceps CSA due to the strength training intervention using HMF versus data from ultrasound, respectively. Improved accuracies in the assessment of muscle size compared to preliminary studies (i.e. more than 70% accuracy in muscle volume [22]) are expected through the additional data from anthropometric measurements and the matching of generic model to the study-specific population group including gender.

2.2 Primary and secondary endpoints

Primary Endpoint: Changes in muscle strength in the lower limbs following the 8-week strength training intervention of the lower limbs in three study groups with different training volumes. The two strength-specific primary outcome parameters are: 1RM and H:Q ratio. Changes in 1RM and H:Q ratio will be derived using the *iOS Strength Control app* and biomechanical analysis before and after the strength training intervention. Primary outcome parameters will be compared between the three study groups in relation to training volumes (Group#1: no training, Group#2: 1 training per week, Group#3: 3 trainings per week). The accuracy in the prediction of 1RM and H:Q ratio will be compared with data from isokinetic strength tests as gold standard.

Secondary Endpoint: Changes in muscle size of the lower limbs following the 8-week strength training intervention of the lower limbs in three study groups with different training volumes. The two secondary outcome parameters are: muscle volume and CSA. Changes in muscle volume and CSA will be derived using the HMF technique in combination with data from 3D body surface scanning and anthropometric measurements before and after the strength training intervention. Secondary outcome parameters will be compared between the three study groups in relation to training volumes (Group#1: no training, Group#2: 1 training per week, Group#3: 3 trainings per week). The accuracy in the derivation of muscle volume and CSA using the HMF technique will be assessed using data from MRI and ultrasound as gold standard.

Key baseline factors that will likely influence the primary and secondary endpoints are strength training experience and gender. The sample size and population group are specified to allow the analysis of gender-specific differences on study results. Thereby, the inclusion/exclusion criteria and study protocol, including a training-related questionnaire, are defined to minimize the bias of training experience.

2.3 Project design

This project in sports science is designed as a confirmatory qualitative study in applied research involving healthy participants. The rationale of this project is to predict changes in muscle strength and muscle size due to strength training using computational modelling and mobile monitoring technology. In particular, we will advance novel approaches in subject-specific anatomically-based modelling and mobile monitoring, which we have previously tested in the research setting, and are now being applied to an intervention study in healthy volunteers to predict adaptations in muscle strength and muscle size in relation to strength training volume.

Study design: The specifics of the strength training intervention are carefully designed based on the current state of research in the field, and in line with strength training recommendations in musculoskeletal health, fitness and rehabilitation. In particular, we will conduct an 8-week strength training intervention program of the key muscle-tendon groups associated with knee joint stability (hamstrings, quadriceps and triceps surae), with the study group (n=36, with 18F and 18M) being randomly allocated to different levels of training volume (Group#1: no training, Group#2: 1 training per week, Group#3: 3 trainings per week) with the same number of subjects and gender distribution in each group. Each participant will perform the strength training self-directedly in their chosen training-specific setting. Clear guidelines for warm-up, type and conduct of exercises will be given to all participants. The strength exercises are standard exercises for strengthening knee extension and flexion: squats, leg press, back extensions, heel raises, and single joint exercises.

Study parameters: Anthropometric parameters include body height, body weight, segmental circumferences, somatotype, body shape, muscle CSA and muscle volume of the lower limbs. Anthropometric parameters will be assessed by means of HMF fitting in combination with data from 3D body scanning and anthropometric measurements according to ISAK standards. Changes in CSA of the hamstrings and quadriceps will be compared between HMF and data from ultrasound before and after strength training intervention. Strength- and training-specific parameters include joint motion, joint acceleration, total joint moments, repetition count, 1RM and H:Q ratio. Strength- and training-specific parameters will be assessed by means of biomechanical analysis using data from optical motion capture and the *iOS Strength Control app,* and compared against data from isokinetic strength tests as gold standard. Additionally, data from MRI of the lower limbs will be acquired in a sub-group of 12 participants (6F, 6M), who will be scheduled for one visit to the imaging facilities of the Swiss Centre for Musculoskeletal Imaging (SCMI) at the Balgrist Campus Zurich. The SCMI provides a highly specialized open access musculoskeletal imaging infrastructure, with a 7T Magnetom Terra and 3T Magnetom Prisma MRI device (Siemens) that can be booked per hour, including imaging support through a professional radiographer. Scan parameters are defined in line with previous research by our group [21]. Participants will be reimbursed for travelling costs.

This is a single-centre study that will be conducted at the research facilities of the ZHAW.

3 PROJECT POPULATION AND STUDY PROCEDURES

3.1 Project population, inclusion and exclusion criteria

Project population: The project population are healthy adult subjects who are all participating in their own strength training program on a regular weekly basis. The primary objective is to predict changes in muscle strength (i.e. primary outcome parameters: 1RM and H:Q ratio) following different training volumes of key muscle groups associated with knee joint stability. A power analysis was conducted using statistikguru.de to assess the required sample size for the primary outcome parameter, 1RM. A Cohen's of d=1.5 was assumed based on previously reported changes in absolute and relative strength following an 8-week strength training intervention in 19 professional rugby league players, with reported changes in squat 1RM pre: 170.6±21.4 kg, post: 200.8± 19.0 kg, $p < 0.001$; and squat 1RM/(body weight) pre: 1.78 ± 0.27 kg·kg^{-1}, post: 2.05 ± 0.21 kg·kg^{-1}, $p < 0.001$; respectively [52]. Given 3 study groups, alpha was set at 0.025. With a

power of 0.9, the required sample size is 11 participants per study group for drawing statistically significant conclusions. Based on the power analysis, we aim for a total of *n=36* complete data sets (*n=12* per study group of the strength training intervention), with a sub-group of *n=12* participants additionally scheduled for MRI of the lower limbs at baseline.

The MRI-based assessment of muscle volume for validation of the HMF technique is analyzed independently from the strength training intervention. Thereby, the accuracy of the HMF technique is dependent on the initial generic musculoskeletal model that is used for model fitting, as well as the available subject-specific skin surface and anthropometric data. The level of significance in the difference of muscle volume between HMF and MRI is expected to vary across muscle-tendon groups, as well as between population groups and gender. In particular, no significant differences were found in the predicted volume of semitendinosus and semimembranosus as part of the hamstrings between HMF and MRI in 5 children without CP (MRI 5.1 (0.91) versus HMF 5.0 (0.30) cm^3/kg, p-value >0.05) and in the predicted volume of the quadriceps, including vastus lateralis, medialis, intermedius and rectus femoris, in 6 children with CP (MRI 15.9 (3.20) versus HMF 16.5 (2.58) cm^3/kg, p-value > 0.05), respectively [22]. Based on previous research, it can be expected that additional consideration of somatotype from anthropometric measurements will help to improve model fit by allowing to adjust the relative thickness of the skin layer, and thus segmental inertia properties, via the HMF objective function for individual subjects. Furthermore, it is very likely that the accuracy in fitting results will be improved when fitting a generic musculoskeletal model to subjects of similar age and gender, and without significant musculoskeletal impairments, which will be the case in the present study. Further details to the MRI-based analysis are provided in Subsection 3.3.

All participants have to confirm their voluntary participation with a written informed consent before being submitted to any study procedure.

Inclusion criteria (all participants, *n=36*):

- Healthy participants; and
- Age 18-40 years old; and
- No acute or chronic musculoskeletal symptoms or pain; and
- Experience with strength training (at least 1-year strength training experience with one training session per week or more); and
- Familiar with strength exercises of key msucles associated with knee joint stability.

Exclusion criteria (all participants, *n=36*):

- Acute or chronic musculoskeletal pain; and/or
- Musculoskeletal surgery within the last 12 months; and/or
- Ongoing rehabilitation or treatment of musculoskeletal complaints or injury; and/or
- Neuromusculoskeletal disease (e.g. cerebral palsy); and/or
- Pregnancy.

Additional inclusion criteria (sub-group of participants, *n=12*):

- No metallic implants
- Comfortable being inside the MRI tunnel for 10-15 min (no history of claustrophobia).

Justification: The design of the strength exercises and participant requirement of at least 1-year strength training experience is based on the expertise of the PI in strength training research involving healthy participants [30, 31, 38-41, 45]. The age cut-off at 40 years is defined in order to avoid co-founding factors between genders due to age-related changes of the musculoskeletal system in females following menopause, i.e. reported decline in muscle mass and strength due to a decline in oestrogen [47]. The additional inclusion criteria for the sub-group of *n=12*

participants are to minimize image artefacts or incomplete datasets due to metallic implants or claustrophobia, as well as measurement bias in the direct assessment of muscular strength.

3.2 Recruitment, screening and informed consent procedure

Participants are recruited through the professional network of the researchers involved. Consecutive ongoing recruitment will take place at the ZHAW through the physiotherapists at the in the Departement of Health Science. A general notice about the study and possibility to participate will also be placed in surrounding fitness centres.
All participants can freely decide to participate in this project, and it will be ensured that there is no dependency between participants and research staff. If an individual expresses interest in participating in this study, a visit to the strength training facilities at the ZHAW will be scheduled via email or phone. During the first visit, the lead investigator will 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 will be informed that the participation in this study is voluntary and that she/he may withdraw from the study at any time without negative effects.
All participants will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participants to make an informed decision about taking part in this study. Inclusion and exclusion criteria will be clarified by asking potential participants for self-declaration. Participants can ask questions and ample time for consideration will be given to each participant to decide whether to participate or not. A pregnancy test will be scheduled for female participants prior to being considered for additional MRI data acquisition.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure. The consent form will be signed and dated by the investigator or his designee at the same time as the participant signs the form. A copy of the signed informed consent form will be given to the study participant. The consent form will be retained as part of the study records. Participants do not obtain any compensation besides the travel costs.

3.3 Study procedures

Project start: May 2021

Project end: May 2025

The overall plan of this 4-year project is given in Table 3.3.1; the schedule of assessment is given in Table 3.3.2; and a summary of all project visits in Table 3.3.3, respectively.

The study protocol consists of three phases, including three visits to the research and training facilities of the ZHAW for all participants, as well as an additional visit to the MRI facilities of the SCMI for a sub-group of 12 participants. The total duration of the study-related visits is 9 hours for *n=36*, and an additional 0.5h for the 12 participants who are scheduled for MRI.

<u>PHASE A: Screening, informed consent & baseline measurements.</u>

- **1st Visit:** Screening, informed consent, health- and training-related questionnaire, allocation into three study groups (Group#1: no training, Group#2: 1 training per week, Group#3: 3 trainings per week). The approximate duration of the 1st Visit is **1h**.
- **2nd Visit:** Baseline measurements. 3D body surface scan, anthropometric measurements, ultrasound, isokinetic strength tests, iPhone/watchOS measurements and optical motion capture during exercise execution. The approximate duration of the 2nd Visit is **4h**. The time between the 1st and 2nd visit is defined within two weeks of the 1st visit to fit in with the participant's schedule.
- **MRI scan** (sub-group, *n=12)*: An additional visit is scheduled for the sub-group of *n=12* participants to obtain data from MRI of the lower limbs. The scan time is 10-15 minutes, with the total duration of the visit to the MRI facilities at the SCMI being approximately **30**

minutes. MRI data acquisition is individually defined within two weeks of the 1st visit to fit in with the participant's schedule.

PHASE B: 8-week strength training intervention. Conduct of an 8-week strength training intervention of key muscle-tendon groups associated with knee joint stability in the training-specific setting of each participant. Participants are randomly allocated into three study groups with increasing levels of loading (Group#1: no training, Group#2: 1 training per week, Group#3: 3 trainings per week) with the same number of subjects and gender distribution in each group (*n=12* per group, 6F and 6M). The same guidelines for the warm-up and the type of exercises will be given prior to the intervention study to each participant. Participants are asked to record exercise load and volume as well as monitor training-related variables and 1RM using the *iOS Strength Control app*. Participants perform the strength training self-directedly in their chosen fitness/training facilities as it fits into their weekly routine. Contact to the study investigator is ensured at all times in case of questions.

PHASE C: Post-intervention measurements.

- **3rd Visit:** The same measurements as at baseline (2nd Visit) will be taken after the strength training intervention, following the same protocols so that the key outcome parameters can be compared before/after training. The approximate duration of the 2nd Visit is **4h.** The 3rd visit is defined within 7 days following the 8-week strength training intervention.

All the procedures in this study are standard procedures in athlete performance monitoring and musculoskeletal health & sports science. 3D body surface data are taken with the participant standing in neutral standing position using a structured light body surface scanner at the ZHAW, taking only a few seconds with extremely high accuracy between the scanned and the actual body volume without requiring any physical contact [37]. Strong in-house support is provided by the department of physiotherapy, at the ZHAW for access and expertise with isokinetic tests, ultrasound and anthropometric measurements according to ISAK standards. Kinematic data will be recorded simultaneously from the iPhone/watchOS and synchronised to a 3D motion capture system (10 camera Vicon System, Oxford Metrics Group, UK). A laptop is used that connects via Bluetooth with the mobile measurement devices, and has the required software for data acquisition and analysis [33]. The set of exercises are standard exercises for strength training, and instructions are given according to established guidelines (see Table 3.3.2). The order of exercises and 3-minute rest interval between exercises are defined to minimise the effects of muscular fatigue on the study results.

MRI scans from pelvis to the toe with the participants lying supine with straight legs are done at the SCMI with support from a professional radiographer (facilities, including technical support are booked by hour) in line with previous research by our group [21] (Scan parameters: TR-TR-3690 ms, TE-67 ms, Slice thickness 4 mm, base resolution 320, gap between slices 10 mm, approximately 70 pictures, 6.5 s per picture). The total scan time is approximately 10-15 min. The chosen values of 4 mm for slices thickness and 10 mm gap between slices are the minimum number of images possible to ensure sufficient images for deriving subject-specific muscle-tendon lengths and volumes of each participant.

Derivation of muscle volume and CSA based on MRI and computational modelling will be done using the open-source modelling environment OpenCMISS (www.opencmiss.org). OpenCMISS is an interactive computational modelling environment for Continuum Mechanics, Image analysis, Signal processing, and System identification, which has extensively been used for high-order subject-specific modelling of the musculoskeletal system. It provides generic model libraries, numerical algorithms and image processing tools for anatomically-based modelling and biomechanical analysis of muscle-tendon deformation [20-22]. Thereby, the present study will extend on previous efforts to derive muscle volume using the HMF technique by adjusting the HMF objective function to incorporate subject-specific thickness of the skin layer based on anthropometric measurements, as well as better matching of the generic musculoskeletal model to the target population group (i.e. age group and gender). For validation purposes, muscle

boundary surfaces will be manually segmented from the MRI data and muscle volumes will be derived by performing numerical quadrature over the parameterised muscle boundary surfaces. The resulting muscle volumes of hamstrings, quadriceps and triceps surae will be compared between MRI and the fitted results from HMF; while data from ultrasound will provide means to validate the accuracy of the predicted adaptation in CSA of hamstrings and quadriceps due to the strength training intervention.

Digital data is safely stored on the secured server architecture at the ZHAW with restricted access to study staff only (see also Section 7). Collected material, including signed consent forms and participant identification list, are safely stored at the ZHAW in locked cabinets. Expected biases to the project include gender, subject-specific training expertise and skin marker artefacts during optical motion capture. The sample size and population group are specified to allow the analysis of gender-specific differences on study results. Thereby, the inclusion/exclusion criteria and study protocol, including a training-related questionnaire, are defined to minimize the bias of training experience; and the functional calibration procedure, that will be employed in this study for optical motion capture, has been show to minimise the effect of skin marker artefacts on kinematic analysis results [15, 48].

Table 3.3.1. *Overall project plan, starting in first quarter of year 1 (May 2021)*

	YEAR 1				*YEAR 2*				*YEAR 3*				*YEAR 4*			
Technology set-up and preparation																
Recruitment																
Data acquisition																
Data analysis																
Project management & reporting																

Table 3.3.2. *Schedule of assessments*

Time (weeks)	***>-1 day***	***0***	***0-2***	***0-2***	***8-10***
Goal	*Info*	*Screening*	*Baseline*	*MRI*	*Post-intervention*
Oral and written information	**+**				
Check inclusion-/exclusion criteria		**+**	**+**		**+**
Written consent		**+**			
Participant characteristics		**+**			
Health- & training-related questionnaire		**+**			
Anthropometric measurements ISAK			**+**		**+**
3D body surface scan			**+**		**+**
Ultrasound measurements			**+**		**+**
Isokinetic strength tests			**+**		**+**
iPhone/watchOS			**+**		**+**
Optical motion capture			**+**		**+**
MRI				***+ (n=12)***	

Table 3.3.3. *Summary table listing all project visits, duration, measurements, procedures and instructions to the participants.*

TIME	MEASUREMENT	PROCEDURE/EXERCISE	INSTRUCTIONS
1st Visit: Screening & informed consent *(n=36)*			

1 h	Informed consent Health- and training-related questionnaire	Inform about study protocol in detail, answer questions, check inclusion and exclusion criteria, assign participant ID, fill in health- and training-related questionnaire.	Participant to carefully read through informed consent and take time for questions and consideration to participate in this study. Participant to fill out consent form and questionnaire.
2nd Visit and 3rd Visit: Baseline measurements & post-intervention measurements *(n=36)*			
4h	Welcome	Outline procedure and double-check inclusion/exclusion criteria. Withdraw participant if health situation has changed.	Participant self-declares inclusion/exclusion criteria.
	Anthropometric data	Anthropometric measurements according to ISAK standards. 3D body surface scan in relaxed neutral position and image capture from frontal and lateral. Ultrasound of hamstrings and quadriceps according to established protocols at the Swiss Olympic Medical Centre	Participants to stand upright on marked location in relaxed neutral position. 3D body surface scan takes 5-10minutes. The participant is asked to stay as still as possible. Participants to sit upright with their lower limbs relaxed and supported in extended position.
	Warm up	Preparation for strength assessment and kinematic data acquisition	Participant performing individual warm up of 5-10 minutes on rower or bike.
	Isokinetic tests	Isokinetic tests according to established protocols at the Swiss Olympic Medical Centre.	Participants performs the standard isokinetic test for hamstring and quadriceps on a commercial testing machine.
	Functional calibration	Measurement set-up and conduct of functional calibration and synchronisation of Apple Watch, iPhone and Vicon system.	Participant to stand upright in relaxed neutral position for attachment of reflective skin markers and Apple watch. Participant to perform set of standard movements for functional calibration.
	Exercises for the assessment of strength- and training-specific data	Forward lunges	Participant to stand upright and move into a lunge position with the front leg. Keep back straight and head upright. Initiate upward movement before the rear knee touches the ground [43].
		Side lunges	Participant to stand upright and move into a side lunge position. Keep back straight and head upright. Shift weight back into neutral standing position and alternate to other side.
		Squat	Participant to stand upright with feet hip-width apart and slightly pointing out. Make sure not to bend forward but keep back straight and knees pointing out in direction of toes.
		Drop jumps	Participants jump from a 30cm box onto the ground and stand still after landing [41].
		Counter-movement jumps	Participant to stand upright, dynamically move into a squat position followed by a vertical jump as high as possible.
		Side-step cutting movements	Participants sprints forward and changes the direction with a cutting side step to the left respectively the right side.
	Dismissal	Participant is shown preliminary results and is informed about further research process.	Participant is given time to look at data and ask questions. Outlining of further study process and thank you for participation.
4rd Visit: MRI of the lower limbs *(n=12)*			

0.5 h	Welcome	Outline procedure and double-check inclusion/exclusion criteria. Pregnancy test for female participants. Withdraw participant if health situation has changed.	Confirm inclusion/exclusion criteria and time for questions.
	MRI data	Scan to be taken at the SCMI Balgrist Campus Zurich using the 7T Magnetom Terra (Siemens) that can be booked per hour, including imaging support through a professional radiographer.	Participant asked to lie on her/his back on bed which is slid into the scanner. Asked to lie as still as possible during the scan (approx. 10min). Participant in voice contact with radiographer at all times and emergency button in reachable distance to stop the scan immediately should participant feel uncomfortable.
	Dismissal	Participant is shown preliminary results and is informed about further research process.	Participant is given time to look at data and ask questions. Outlining of further study process and thank you for participation.

3.4 Withdrawal and discontinuation

Participants can withdraw from the study at any time without giving further reasons. A participant can also be withdrawn from the study if she or he does not comply to the instructions of the study personnel as outlined in Table 3.3.3 or the participant's health situation has changed between the initial screening and the training session due to unforeseen circumstances (i.e. exclusion criteria: acute musculoskeletal pain or injury).

If a participant is withdrawn from the study (or withdraws by herself/himself) during the schedule of assessments, only data gathered up to the point of withdrawal will be used for analysis.

All personal data is encrypted by assigning a unique participant ID to all experimental raw data and electronic data sheets, including analysis results. All data is stored on the secured server architecture at the SFSIM with restricted access to study staff only (see also Section 7).

4 STATISTICS AND METHODOLOGY

4.1. Statistical analysis plan

Statistical analysis will be conducted with SPSS (SPSS v. 21, IBM, USA) after consultation with a statistician in line with previous research by our group.

For the Primary Objective, a repeated measures analysis of variance (ANOVA) will be conducted to assess statistically significant differences between the predicted values of 1RM and H:Q ratio from biomechanical modelling and mobile monitoring with the measured values from optical motion capture and isokinetic strength tests following the 8-week strength training intervention. A correlation analysis will be done to relate the strength-specific outcome parameters to the training-specific parameters for each study group. Principal component and factor analysis will be performed to identify correlations between strength-specific and training-specific parameters.

For validation of the HMF technique, we will follow the statistical methods of previous research by our group [21, 22] to assess the significance in the differences of muscle volume between HMF and MRI, as well as the difference of the predicted adaptation in CSA between HMF and ultrasound. The level of significance in the difference of muscle volume between HMF and MRI is expected to vary across muscle-tendon groups and gender. In particular, no significant differences were found in the predicted volume of semitendinosus and semimembranosus as part of the hamstrings between HMF and MRI in 5 children without CP (MRI 5.1 (0.91) versus HMF 5.0 (0.30) cm^3/kg, p-value >0.05) and in the predicted volume of the quadriceps, including vastus lateralis, medialis, intermedius and rectus femoris, in 6 children with CP (MRI 15.9 (3.20) versus

HMF 16.5 (2.58) cm^3/kg, p-value > 0.05), respectively [22]. It is expected that the accuracy in the predicted muscle volume is improved in the present study by fitting a generic musculoskeletal model to subjects of similar age and gender, and without significant musculoskeletal impairments, as well as additionally considering subject-specific somatotype based on anthropometric measurements. ANOVA will be performed to analyse the pairwise differences in muscle volumes between the HMF and MRI-based results; and to analyse the pairwise differences in the predicted adaptation of hamstrings and quadriceps CSA between HMF and data from ultrasound before and after strength training intervention, respectively. The data from female and male participants will be analysed combined, as well as independently as two different groups.

The level of significance will be set at $p<0.05$ for all statistical tests.

4.2. Handling of missing data

As a single-centre study, this project has a low risk for missing data. All data will be recorded and safely stored on site. All efforts are being made with safety procedures in place not to lose any data during lab visits. In case of technical problems during data acquisition, the measurements will be repeated on the spot. In case of incomplete datasets due to withdrawal or drop-out, additional participants will be recruited until an adequate number of complete datasets (i.e. *n=36* for primary endpoint, *n=12* for secondary endpoint) are obtained.

5 REGULATORY ASPECTS AND SAFETY

5.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, Good Clinical Practice, the Clinical Trial Ordinance (ClinO) as well as other locally relevant legal and regulatory requirements. The study will be registered at the Swiss National Clinical Trials Portal (SNCTP).

5.2 (Serious) Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavorable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	Description

Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigator and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study.

If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the Investigator reports it to the Ethics Committee via BASEC within 15 days.

Follow up of (Serious) Adverse Events

All (S)AEs will be followed up until resolution or until the condition has stabilised with no further change expected.

Notification of safety and protective measures (see ClinO, Art 62, b)

If immediate safety and protective measures have to be taken during the conduct of the study, the investigator notifies the Ethics committee of these measures, and of the circumstances necessitating them, within 7 days.

5.3 (Periodic) safety reporting

An annual safety report (ASR/DSUR) is submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs).

5.4 Pregnancy

Pregnancies will be reported within a maximum of 24 hours to the Sponsor-Investigator. The occurrence of pregnancy will be handled by withdrawing the patient from the study and outcome of the pregnancy is followed up.

5.5 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations

shall be documented and reported to the Ethics Committee as soon as possible. Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29). A list of all non-substantial amendments will be submitted once a year to the competent EC together with the ASR.

5.6 (Premature) termination of study

The Sponsor-Investigator may terminate the study prematurely in case of alterations in accepted clinical practice that make the continuation of the study unwise.

Upon regular study termination, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38). Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38). The appropriate template concerning the notification of completion, discontinuation or interruption of the clinical trial available at www.swissethics.ch will be used.

5.7 Insurance

In the event of study-related damage or injuries, the liability of the ZHAW provides compensation, except for claims that arise from misconduct or gross negligence.

6 FURTHER ASPECTS

6.1 Overall ethical considerations

The burden and time effort for participants is small, and the potential for continuous research and relevant health care improvements based on the advanced computational, biomechanical and mobile monitoring technologies are given. Voluntary study participation is ensured at all times. Given that participants are required to have at least one year of strength training experience with a minimum of one training session per week, the time requirement and burden from the measurements is fair and not interfering much with their usual sports routine. Insights gained from the study results, including anthropometric, strength-specific and training-specific outcome parameters, will be shared with participants and may likely benefit individual sports practice. In the event that an incidental finding is detected, the participant will be informed of this and will be referred back to her/his general practitioner. However, participants will be informed that the acquired data, including MRI data, will not be read by medical staff (e.g. radiologist).

The expected advancement in subject-specific musculoskeletal modelling and mobile monitoring tools, resulting from this study, are greatly outweighing the minimal risk for participants. The study objectives are addressing key limitations that are highly relevant within the global fields of sports science, orthopedics and biomechanics research, and are crucial towards driving future digital twin and human health models. The application of research outcomes will not only benefit athletes but there is tremendous potential also in advancing community-based initiatives and public health services by informing and supporting safe and effective strength training practice. In Switzerland, more than 1.3 Mio people are member of a fitness center [50], and the World Health Organization (WHO) have included strength training in their recommendations for health, with physical inactivity identified as the fourth leading risk factor for global mortality [51]. The use of smartwatches and user-friendly software applications will not only help clinicians and physiotherapists to track training volume once the patient leaves the clinic, but it may also provide a valuable tool to ensure correct adherence to training guidelines.

6.2 Risk-Benefit Assessment

The overall risk for participants is minimal, with the risk of harm due to the procedure itself being minimized by the design of the protocol. All the methods and techniques that are used for data collection are non-invasive and based on standard protocols in athlete performance monitoring and musculoskeletal health & sports science.

The training routine of each participant will be discussed and only participants who are familiar with the proposed set of strength exercises will be included. The strength exercises are identical with the exercises that are being performed in usual fitness and rehabilitation routines. The risk of musculoskeletal injury is equivalent to the risk during their standard strength training routine. IMU measurements and optical motion capture require small reflective markers or devices (watchOS) to be attached to the body surface. Possible skin irritations are very rare and can be locally treated (creams).

Only a sub-group of n=12 participants is recruited for MRI of the lower limbs. This is because MRI is costly and MRI-based subject-specific musculoskeletal modelling is very time consuming. There are minimal additional risks and time burden (i.e. 0.5h) for participants who are undergoing MRI. MRI is the gold standard technique for musculoskeletal imaging without exposing the subject to harmful radiation [38]. In case a participant feels uncomfortable inside the MRI tunnel due to claustrophobia or other reasons, the imaging can be discontinued anytime. The same holds for 3D body surface scanning, ultrasound, isokinetic strength tests and marker-based optical motion capture, should a participant feel uncomfortable or exhausted. Participants will be offered to rest at the research and training facilities of the ZHAW during and after different types of measurements to minimize risk of fatigue or injury.

The risk of unauthorized data access and/or unwanted identification of project participants is minimized through ensuring safe data recording and storage procedures (as detailed in Section 7). The health- and training-related questionnaire is not known to be related to any risks as it does not include any psychiatric questions that could traumatize.

Direct benefits for participants may include enhanced knowledge about individual body shape, body composition and muscular strength with improved guidelines for strength exercise execution. Indirectly, their contribution will greatly benefit community-based and global research efforts in personalized health care and sports practice (as outlined in Section 6.1).

7 QUALITY CONTROL AND DATA PROTECTION

7.1 Quality measures

The project leader and senior post-doctoral scientist will oversee the study conduct from recruitment to final analysis and reporting of study results. They are both trained on all important project-related aspects, planned quality visits and independent data review; and will be supervising the PhD student who is involved in this project. Experienced research and clinical staff at the ZHAW and the SCMI be involved to ensure all measurements, data processing and analysis is done efficiently to minimise time and risks involved for participants and ensure the best possible quality to maximise the scientific gains.

Strict adherence to study protocol, including the use of standardised case-report forms, will ensure correct and complete data collection and monitoring. Monthly data quality monitoring sessions will be scheduled to oversee the data collection process and ensure the achievement of primary and secondary objectives. Study-specific quality control of informed consent and quality of recorded data will be done by the PI. Quality control of measurement devices and technologies, measurement procedures and data storage and management will be done through established quality control procedures and responsible staff at the SCMI.

The PI will be responsible for ongoing quality control and proper training of all involved study personnel. The Ethics Committee may visit the research sites for quality assurance. Direct access to the source data and all project related files and documents must be granted on such occasions.

7.2 Data recording and source data

Signed informed consent forms and participant identification lists are stored in paper form in locked cabinets at the ZHAW, Technikumstrasse 9, 8400 Winterthur.

The following source data is recorded, handled and stored (enabled version history and track changes):

Informed consent:	paper / at ZHAW, 8400 Winterthur
Patient identification list with contact information:	paper / at ZHAW, 8400 Winterthur
Basic demographics:	electronically via REDCap / ZHAW server
Health- and training-specific questionnaire:	electronically via REDCap / ZHAW server
Anthropometric data:	electronically via REDCap / ZHAW server
3D body surface data:	electronically / ZHAW server
Ultrasound data:	electronically / ZHAW server
Isokinetic strength data:	electronically / ZHAW server
IMU data from Apple Watch:	electronically / ZHAW server
Marker trajectories from optical motion capture:	electronically / ZHAW server
MRI data:	CDROM / at ZHAW, 8400 Winterthur electronically / ZHAW server

All experimental data are saved in a coded electronic database and encrypted using a unique individual participant ID according to swissethics guidelines (birth year plus coded number). This holds true for all raw data as well as the results from the data analyses. After data collection, the raw data will be transferred into the HFG-conform coded electronic database that is stored on the secured server architecture at the ZHAW with limited access to project staff only (see also section 7.3). Data from MRI will be provided by the SCMI on CDROM in encrypted format, which is common practice in medical imaging. CDROMs will be stored in the locked cabinets at the ZHAW,Technikumstrasse 9, 8400 Winterthur.

7.3 Confidentiality and coding

Project data will be handled with uttermost discretion and is only accessible to authorized personnel who require the data to fulfil their duties within the scope of the research project. On the CRFs and other project specific documents, participants are only identified by a unique participant number. Participants can withdraw from the study at anytime. The data that was acquired up to that point will be analyzed in encrypted format. The data from participants who have withdrawn from the study will be anonymized following the completion of the data analysis. The participants' identification list will be destroyed so that nobody can trace back to the original identities of the participants. This is to ensure data security.

The acquired data will be kept in computer memory and on CDROM during and after completion of the study and will only be accessible to study investigators. The consent forms will be safely stored according to Art 62 KlinV.

All data is stored on the HFG-conform servers of the ZHAW with restricted access to study staff only (login/username & password). Authentication information is transmitted securely using HTTPS. Passwords are stored using crypt hashes. The system uses a role-based authorization scheme, where each user has to be assigned at least one role. A study-specific, secured space will be created by the PI as part of the server architecture at the ZHAW, which has all necessary software security system application to establish an HFG-conform database according to Art. 18 KlinV, allowing for file version documentation, and all additions, deletion and changes to that data are tracked in an audit trail, documenting old value, new value, user name and timestamp.

Routine backups are done within the framework of the established server architecture setup to prevent data loss.

7.4 Retention and destruction of study data and biological material

All measurement data will be stored for 10 years after the end of the project following strict guidelines in Good Clinical Practice. Electronic data is stored within the secure server architecture of the ZHAW. Informed consent forms, participant identification list and CDROMs are stored at the ZHAW in locked cabinets.

8 FUNDING / PUBLICATION / DECLARATION OF INTEREST

This project is funded through project funding from the Swiss National Science Foundation (SNF).

The PI and senior project staff are committed to delivering high-level scientific and technological results and provide novel interdisciplinary research opportunities for young researchers. The primary and secondary outcomes will be summarized and published in peer-reviewed scientific journals, as well as presented at international conferences to disseminate the knowledge gained from this study. Open-source access to the encrypted data from this project will be considered following strict data sharing policies and international guidelines in good clinical practice to benefit the wider research community.

There are no conflicts of interests.

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