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**Hypertension and retinal microvascular dysfunction
(HyperVasc): Protocol of a randomized controlled exercise
trial in patients with hypertension**

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-058997
Article Type:	Protocol
Date Submitted by the Author:	07-Nov-2021
Complete List of Authors:	Streese, Lukas; University of Basel, Department of Sport, Exercise and Health Gander, Joséphine; University of Basel, Department of Sport, Exercise and Health Carrard, Justin; University of Basel, Department of Sport, Exercise and Health Hauser, Christoph; University of Basel, Department of Sport, Exercise and Health Hinrichs, Timo; University of Basel, Department of Sport, Exercise and Health Schmidt-Trucksäss, Arno; University of Basel, Department of Sport, Exercise and Health Gugleta, Konstantin; University of Basel, Department of Ophthalmology Hanssen, Henner; University of Basel, Department of Sport, Exercise and Health
Keywords:	Hypertension < CARDIOLOGY, SPORTS MEDICINE, CLINICAL PHYSIOLOGY

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Manuscripts

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3 **Hypertension and retinal microvascular dysfunction**
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5 **(HyperVasc): Protocol of a randomized controlled exercise trial**
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7 **in patients with hypertension**
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Abstract

Introduction: Hypertension is a global health care burden that affects the structure and function of the macro- and microcirculation and induces disease-specific end-organ damage. Vascular biomarkers are essential to timely diagnose this end-organ damage to improve cardiovascular (CV) risk stratification and medical decision making. Exercise therapy is an effective means to improve vascular health and reduce overall CV risk. However, it is still not clear whether high-intensity interval training (HIIT) is recommendable for patients with hypertension to reduce blood pressure, increase cardiorespiratory fitness and ameliorate vascular health.

Methods and analysis: The “Hypertension and retinal microvascular dysfunction” (HyperVasc) trial will investigate macro- and microvascular impairments in hypertensive patients compared to healthy controls to investigate hypertension-induced end-organ damage by using gold-standard methods as well as newly developed unique retinal microvascular biomarkers. In addition, this trial will investigate the reversibility of retinal end-organ damage by assessing the effects of an eight-week supervised and walking based HIIT on blood pressure, cardiorespiratory fitness as well as macro- and microvascular health, compared to a control group following standard physical activity recommendations. Further outcomes will be microalbuminuria, hypertensive retinopathy, and classical CV risk markers. Analysis of variance and analysis of covariance will be used to investigate group differences between healthy controls and hypertensive patients and training effects in hypertensive patients, respectively.

Ethics and dissemination: The Ethics Committee of Northwestern and Central Switzerland approved this study (EKNZ-2021-00086). All participants will give informed consent.

Registration details: The HyperVasc study was registered in February 2021 on ClinicalTrials.gov: NCT04763005.

Strengths and limitations of this study:

- The HyperVasc trial will investigate, for the first time, hypertension-related macro- and microvascular impairments by using newly developed non-invasive techniques of retinal microvascular phenotyping.
- The results of this study will 1) improve the understanding of microvascular impairments in hypertensive patients, 2) improve the knowledge of exercise-induced macro- and microvascular remodelling, and 3) highlight the potential of retinal vessel

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3 imaging for cardiovascular risk stratification and therapy monitoring in patients with
4 hypertension to improve medical decision making in a personalised medicine approach.
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For peer review only

Introduction

Arterial hypertension is a growing global health care burden. The number of hypertensive patients is predicted to increase globally to 60% by 2025¹. The prevalence in Europe is thought to be about 30-45%, with increasing blood pressure (BP) levels at higher age². About 40% of all annual deaths in Europe are directly related to hypertension-induced cardiovascular (CV) disease³.

Hypertension affects the structure and function of the macro- and microcirculation and leads to advanced vascular ageing. A timely diagnosis of dysfunction beyond vascular ageing allows for improved estimation of individual CV risk and more specific clinical decision making in primary and secondary CV prevention⁴. The European Society of Cardiology Working Group on peripheral circulation has recommended to routinely measure vascular biomarkers for CV risk assessment in all patients⁵.

Different non-invasive techniques to investigate the macro- and microvascular structure and function exist. Flow-mediated dilatation (FMD) is considered to be the gold standard to quantify endothelial function in the macrocirculation⁶. Blunted FMD has been shown to be predictive for CV events⁷ and all-cause mortality⁸. Each unit decrease of FMD was associated with 16% higher risk to develop hypertension⁹. Impaired endothelial function leads to the development of atherosclerosis by increasing arterial wall thickness and plaque formation^{10 11}. Together with markers of central haemodynamics, FMD has become one of the most frequently used vascular biomarker for the evaluation of vascular dysfunction in the macrocirculation.

Microvascular organ damage can be investigated by performing the static (SVA) or dynamic (DVA) retinal vessel analysis, which are both non-invasive techniques and valid biomarkers of vascular health and CV risk¹². Narrower retinal arteriolar diameter equivalents (CRAE), wider venular diameter equivalents (CRVE) and a lower arteriolar-to-venular diameter ratio (AVR) have been associated with a higher risk of stroke¹³⁻¹⁵, coronary artery disease¹⁶ and CV mortality^{17 18}. Retinal arteriolar narrowing is predictive for the development of hypertension and is associated with the severity of hypertension¹⁹⁻²¹.

The method of DVA has the potential to directly and non-invasively investigate microvascular endothelial function by measuring flicker light-induced dilatation (FID) over time. FID is negatively associated with CV risk factors such as age^{22 23}, increased body mass^{24 25}, blood pressure²⁶ or cholesterol²⁷ as well as manifest CV diseases such as diabetes²⁸ or heart failure²⁹. Impaired FID seems to be predictive for non-fatal and fatal CV disease events in high risk cohorts^{30 31}. Every standard deviation decrease in FID reduced all-cause mortality by up to 35%

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3 in end-stage renal disease patients. The reclassification rate of additional FID was 27%
4 compared to standard care in this three-years follow-up study³⁰.
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7 We have recently established normative data and recommendations for standard operating
8 procedures for SVA and DVA¹². In addition, we developed two new methods to improve non-
9 invasive phenotyping in the retinal microcirculation, which have not yet been applied in
10 patients with hypertension^{32 33}. The first new approach allows for the investigation of the wall-
11 to-lumen ratio in retinal arterioles and venules³². By inducing an acute standardized BP rise
12 using a defined hand-grip exercise, we are able to assess the retinal myogenic constriction in
13 addition to and as a counter regulatory mechanism of FID³³.
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16 Lifestyle interventions such as exercise, salt-reduced diet or alcohol reduction can have a
17 significant impact in lowering BP and may have additional health benefits beyond their BP
18 impact³⁴. We have recently shown that physical activity (PA) and exercise improve retinal
19 microvascular health in healthy children and adults, as well as CV risk patients³⁵. In addition,
20 regular PA is effective in reducing BP and evidence suggests that PA can reduce the risk of
21 developing de novo hypertension³⁶. A meta-analysis of 13 prospective cohort studies including
22 more than 135 000 participants confirmed a 19% risk reduction of developing hypertension in
23 individuals with high versus low PA³⁷. PA and high cardiorespiratory fitness (CRF) seem to be
24 beneficial even in hypertensive patients. A study on the combined effects of BP and PA on CV
25 mortality revealed health benefits for individuals with high versus no PA, independent of their
26 BP levels³⁸. Especially, high CRF seems to protect against vascular ageing³⁹⁻⁴¹. Hypertensive
27 patients with high CRF levels demonstrated a lower prevalence of carotid atherosclerosis.
28 High-intensity interval training (HIIT) is an effective method to increase CRF and seems to
29 have superior health benefits compared to moderate-continuous training in healthy⁴² and
30 diseased populations^{43 44}. Costa et al. showed no differences between HIIT and moderate-
31 continuous training interventions on resting BP. However, HIIT showed higher improvements
32 in CRF compared to moderate-continuous training with potential for long-term health benefits
33 for patients⁴⁵. The European Association of Preventive Cardiology and the Council on
34 Hypertension of the European Society of Cardiology have recently summarised the evidence
35 of exercise in the prevention and treatment of arterial hypertension⁴⁶. Endurance training was
36 the first exercise priority for hypertensive patients with an expected BP lowering effect of -4.5
37 to -7.4 mmHg, followed by a combination of endurance and resistance training (-5.3 to -5.6
38 mmHg), isometric (-5.1 to -5.2 mmHg) and dynamic resistance training (-2.3 to -2.4 mmHg).
39 However, the authors noted that the evidence for HIIT as exercise therapy to reduce blood
40 pressure is scarce. Therefore, the HyperVasc study will investigate whether HIIT is a suitable
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3 exercise therapy for hypertensive patients to reduce BP, increase CRF and, improve subclinical
4 retinal microvascular end-organ damage indicating overall vascular risk reduction.
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9 Methods and analysis

10 Study design

11 The “Hypertension and retinal microvascular dysfunction” (*HyperVasc*) study consists of two
12 parts. Part I is designed as cross-sectional study, part II is designed as randomized controlled
13 trial. Twenty healthy and normotensive controls and 40 hypertensive patients are included in
14 part I to investigate group differences in BP, CRF and the hypertension-induced macro- and
15 microvascular end-organ damage. In part II, hypertensive patients are randomized following
16 their baseline assessment into a HIIT group (n=20) or a control group with standard PA
17 recommendations (n=20) to investigate the exercise effects on BP, CRF as well as the macro-
18 and microvascular phenotype (Figure 1). In addition to vascular health, extensive phenotyping
19 including classical CV risk markers is performed. Phenotyping details are described below.
20 The phenotyping as well as the training intervention will take place at the Department of Sport,
21 Exercise and Health (DSBG), Basel, Switzerland. The study is planned and conducted in
22 accordance with the Helsinki Declaration⁴⁷. All participants have to sign a written informed
23 consent, prior to the first assessment. The Ethics Committee of Northwestern and Central
24 Switzerland approved this study (EKNZ-2021-00086). This study has been registered in
25 February 2021 on ClinicalTrials.gov: NCT04763005. Due to Severe Acute Respiratory
26 Syndrome Coronavirus 2 (SARS-nCOV-2) pandemic, all assessments are conducted under
27 consideration of the hygiene recommendations developed by the Task-Force of the University
28 of Basel based on the guidelines of the National Ministry of Health (BAG).

29 Inclusion and exclusion criteria

30 Men and women previously diagnosed with hypertension, receiving drug treatment for arterial
31 hypertension and controlled BP, hypertension grade I is accepted (study threshold: $\leq 159/99$
32 mmHg) as well as normotensive healthy controls (study threshold: $\leq 129/84$ mmHg) between
33 40 and 70 years of age are recruited via advertisements in local newspapers. For BP
34 categorisation, patients are measured on two separate days according to the current 2018
35 ESC/ESH hypertension guidelines⁴⁸. Exclusion criteria for both groups are any CV medication
36 (accept for antihypertensive medication in the hypertensive group), history of CV, pulmonary,
37 or chronic inflammatory disease, active smoking status, body mass index ≥ 30 kg/m², macular
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3 degeneration, glaucoma or any chronic eye disease, exercise-limiting orthopaedic problems,
4 high intraocular pressure (IOP) (≥ 20 mmHg) or changes in antihypertensive medication during
5 the intervention period.
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10 **Anthropometry, blood pressure, physical activity and fitness**

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12 Anthropometric data are measured in the morning under fasting conditions. Height and waist
13 circumference are measured by use of standard procedures. The Inbody 720R (JP Global
14 Markets GmbH, Germany) is used to obtain body mass, body mass index, lean body mass and
15 body fat⁴⁹. Blood samples are drawn by venepuncture of the cubital fossa of the right or left
16 arm by trained staff. Urine samples are taken to measure microalbuminuria in all participants.
17 Blood and urine samples are centrifuged and stored at -80° for further analysis after data
18 acquisition has been completed successfully. BP is measured over 24 hours using the Mobil-
19 O-Graph® 24h pulse wave reflection monitor device (I.E.M GmbH, Germany) with integrated
20 ARCSolver® software. This device measures the peripheral and central haemodynamics as well
21 as the 24h pulse wave velocity (PWV) every 20 minutes during the day and every 60 minutes
22 during the night. IOP is measured with the ICare PRO (Tiolat Oy, Helsinki, Finland) rebound
23 tonometer.

24 Self-reported PA levels are analysed using the Freiburg Questionnaire of Physical Activity⁵⁰.
25 Physical fitness is measured with an individualized bicycle ramp protocol as previously
26 described⁵¹ using the Cortex Metalyzer R 3B metabolic test system (Cortex Biophysik GmbH,
27 Leipzig, Germany) to analyse circulatory and ventilatory parameters including peak oxygen
28 uptake (VO₂peak) and maximal heart rate (HRmax). Individual exhaustion is achieved when
29 participants reach the previously defined respiratory exchange ratio cut-off value of 1.10 for
30 participants between 40-59 years of age and 1.06 for participants between 60-69 years of age⁵².
31 The individual ramp protocol is repeated on a separate day if individual exhaustion is not
32 achieved.

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50 **Macro- and microvascular assessments**

51 All vascular assessments are performed in the morning under fasting conditions. Participants
52 are asked to avoid alcohol and exercise 24h prior the appointment and any food or caffeine
53 intake at the day of the appointment. Only unsweetened water and medication intake is allowed.
54 Investigators are blinded for the patients' characteristics and group allocation in the vascular
55 assessments.

Macrocirculation

FMD is measured with a semiautomatic and ECG-guided high resolution B-mode ultrasound system (UNEX EF 38G, UNEX Corp., Nagoya, Japan) after 15 minutes of rest in a supine position. Measurement takes place in a dark, quiet and temperature-controlled room. The arm of the participants is abducted in a 90° angle in a relaxed position. A 10-MHz H-shaped probe is used to measure the right brachial artery on a short- and long-axis. The device continuously corrects the probe position during the whole procedure to generate the image with the highest quality. A cuff placed at the forearm of the participants (5-10 cm distal to the probe and 1-2cm proximal to the cubital fossa) increases cuff pressure for 5 minutes 50mmHg above the resting BP, measured after 15 minutes of rest in a supine position. Rest diameter of the right brachial artery is measured before cuff-inflation for 10 seconds. In addition, the diameter of the brachial artery is measured continuously during the last 60 seconds of the inflation period and during 3 minutes after cuff deflation to analyse sheer stress induced vascular response.

The 24h PWV is analysed every 20 minutes during the day and every 60 minutes during the night with the Mobil-O-Graph®, in combination with the BP measurement, as described above.

Microcirculation

Conventional eye drops (Tropicamide 0.5%) are used to dilate the pupil of the right eye of each participant. The left eye is used in cases of local eye disease on the right eye. Images of the eye background with the optic disc in the centre using the Dynamic Vessel Analyzer (DVA®; IMEDOS Systems GmbH, Jena, Germany) and a fundus camera (450 FF; Carl Zeiss, Jena, Germany) are taken to assess retinal vessel diameters. Standard operating procedures are used to analyse CRAE, CRVE and AVR as described previously¹² based on three high quality images with an angle of 50°. The retinal vessel microstructure, including the retinal vessel wall and the wall-to-lumen ratio is analysed based on three images with an angle of 20° and a green filter as described previously³². The oxygen saturation of the retinal microcirculation is analysed based on two images with a specific oxygen filter⁵³. A senior ophthalmologist rates the presence and severity of hypertensive retinopathy based on one high-definition image of each participant.

Retinal endothelial function is analysed with the same camera by measuring arteriolar and venular diameters over time with two protocols. The first protocol investigates neurovascular coupling using FID as a marker of retinal, and therefore, cerebrovascular endothelial function. A detailed method description can be found elsewhere¹². The second protocol investigates the

myogenic constriction of the retinal microcirculation, also known as the Bayliss effect. Participants are asked to perform a standardized handgrip exercise to increase their BP, which results in a myogenic constriction of the smooth muscles of the vessels. To standardize the BP increase, the Leonardo Mechanograph GF® device (Novotec Medical GmbH, Pforzheim, Germany) is used to test the grip strength one repetition maximum (1RM) of the left hand. The best value of three attempts is taken as guidance for the handgrip exercise. The BP is controlled beat-to-beat during the whole procedure by using the Finapres® (Finapres Medical Systems B.V., Enschede, Netherlands) device on the middle finger of the right hand. The setup has been described in detail previously³³. The second protocol starts with a 50-second rest phase. This rest phase is used to calculate the baseline diameter. After 50 seconds of rest the participants are asked to press the Leonardo Mechanograph GF® device with the left hand for 30 seconds with 30% of their 1RM. The produced power is controlled with the Leonardo Mechanography BAS v4.4 software. An acoustic signal is implemented to help the participants stay at 30% of their 1RM. A variance of 2% is tolerated. After 30 seconds at 30% 1RM, participants are verbally motivated to press as hard as possible for another 30 seconds (all-out phase) to reach a peak BP increase. A subsequent rest phase of 80 seconds is implemented to investigate the vessel response after myogenic constriction. The vessel diameters of two arteriolar and venular vessel segments are measured continuously during the whole procedure.

Exercise intervention and control condition

Hypertensive patients are randomized to an 8-week HIIT or a control group. The exercise intervention is a supervised and walking-based HIIT (3x/week), starting with a habituation week with an intensity of 75% HRmax. In the following seven weeks, the participants will perform a HIIT based on the following protocol and with a total duration of 45 minutes per session (modified from Wisloff et al.⁵⁴): warm-up for 10 minutes at 60-70% HRmax followed by a high-intensity interval consisting of 4x4 minutes at 80-95% HRmax with 3 minutes of active recovery at 60-70% HRmax and a 10-minute cool-down at 60-70% HRmax. Heart rate will be monitored during training by Polar® H7 heart rate sensors combined with Polar® M400 watches. Sport scientists motivate the participants during the high intensity intervals and will control the heart rate of each participant during and after every training session. This training program has previously been used in CV risk patients with a high adherence and without any drop-out related due to the exercise training⁵⁵. The control group will get PA recommendations and exercise training advices based on current guidelines⁵⁶, the CRF test and the PA

questionnaire. Participants in the control group document their PA behaviour in a PA diary and get a phone call after 4 weeks to evaluate their well-being.

Data management

Investigators are trained by experts in all assessments. Vascular assessments are performed by one experienced investigator to avoid inter-observer variability. Data are stored in a laboratory data base without external access with generated study IDs. Previously selected investigators have access to this database. Only the principal investigator can match names of the participants with study IDs. Data are cleaned and checked for their plausibility at the end of the study. Changes in the database are registered and controlled by an external researcher at the end of the study. This researcher is not involved in planning the study, data acquisition or analysing the data. Auditing during the data acquisition period is not planned but all study entries in the final database will be stored and are replicable at the end of the study. Interim analysis is not planned. Potential drop-outs and their reasons are collected and reported at the end of the study. The study will be stopped immediately if any intervention-induced adverse event occur. Adverse events will be communicated directly to the ethic committee. Drop-out participants are invited to take part in the follow-up assessment where all assessments from visit III are planned (Figure 1). Multiple imputation is used to handle missing data^{57 58}.

Randomization

A blockwise randomization is done to get equal group sizes in the HIIT and the control group. An independent research assistant draws group allocation from a locked envelope to perform randomization after baseline assessments. LS is responsible to communicate the enrolment decision to participants. Sex was the only stratification factor during the randomization process. Participants and sport scientists who supervise the intervention are not blinded for group allocation. Outcome assessors and researchers who analyse data are blinded for group allocation.

Statistical analysis

The primary outcome of this study is the AVR difference between hypertensive patients and normotensive healthy controls in the cross-sectional part (Part I) and among hypertensive patients before and after eight weeks of HIIT compared to the control group (Part II). Secondary

outcomes are BP, VO₂peak, FMD, arteriolar and venular retinal endothelial function, arteriolar and venular retinal myogenic constriction, retinal wall-to-lumen ratio and retinal oxygen saturation. Further outcomes are microalbuminuria, hypertensive retinopathy, classical CV risk markers and further patients' characteristics. Median and interquartile ranges are used to describe patients' characteristics in both parts. Boxplots are used to visualize the primary and secondary outcomes in the cross-sectional and the interventional part. Analysis of variance are used to compare AVR (and secondary outcomes) between patients and healthy peers. For the interventional part, analysis of covariance are calculated to compare AVR (and secondary outcomes) after 8 weeks of intervention between the HIIT and the control group adjusted for the corresponding values at baseline, age, sex and ΔBP⁵⁹. Intention-to-treat principle is used as primary analysis and per protocol as secondary analysis. The statistical program R (R Foundation for Statistical Computing, Vienna, Austria, version 3.5.0.) will be used for the generation of graphs and for statistical tests with a two-sided confidence interval of 95%.

Sample size calculation

Cross-sectional approach:

Based on previous results a mean AVR difference between patients and healthy peers of 0.04 with a standard deviation of 0.04 is expected⁶⁰. To reach a power of 95% with a two-sided significance level of 0.05, a total sample size of 46 participants is needed. To reach the target power in case of missing data, based on insufficient data quality, 20 controls and 40 patients are included in this study.

Interventional approach:

An exercise-induced AVR improvement of 0.03 with a standard deviation of 0.05 is expected, based on our previous publication⁵⁵. A total sample size of 32 participants is necessary to reach a power of 95% with a two-sided significance level of 0.05. Due to possible drop-outs 40 participants in total are included to randomize these participants to 20 patients in the control and 20 patients in the exercise intervention condition. We used G*Power software 3.1.9.2 for the sample size calculation⁶¹.

Patient and public involvement statement

All methods included in this study have been used in previous trials. Participants' feedback is used to select material and methods. Participants are not involved in the study design. However,

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3 participants are asked to take part in the acquisition by communicating the trial with their
4 families and friends. The HIIT is planned to take place at the DSBG. In single cases, the
5 intervention can be performed at home based on participants' availability but controlled by a
6 heart rate sensor and stored on a Polar® M400 watch. Participants will be informed about their
7 individual results directly after their visits and about the overall study results at the end of the
8 HyperVasc study. In addition, all participants get detailed and individualized PA and exercise
9 training advices based on the CRF test and the PA questionnaire to optimize their daily PA
10 behaviour.
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17 18 **Time plan** 19

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21 The acquisition started in February 2021 after the ethical approval and is still ongoing. Last
22 patient out is planned for spring 2022. This is the first and only version of the HyperVasc study
23 plan.
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26 27 **Hypotheses and potential impact** 28

29 The HyperVasc trial will investigate, for the first time, the BP-induced macro- and
30 microvascular impairments in detail by using newly developed techniques of retinal
31 microvascular imaging. Primarily, we expect to find a lower AVR in patients with hypertension
32 compared to healthy controls and a more pronounced arteriolar dilatation and venular
33 constriction amongst further amelioration of the assessed retinal microvascular
34 pathophysiology after 8 weeks of HIIT in patients with hypertension compared to standard PA
35 recommendations. Both hypotheses will be addressed for the secondary and further outcomes.
36 The results of this study will 1) improve the understanding of retinal microvascular
37 impairments in hypertensive patients, 2) enhance the knowledge of exercise-induced macro-
38 and microvascular remodelling, and 3) highlight the potential of investigating retinal
39 microvascular end-organ damage for CV risk stratification and therapy monitoring to improve
40 the medical decision making in a personalised medicine approach.
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50 51 **Ethics and disseminations** 52

53 The Ethics Committee of Northwestern and Central Switzerland approved this study in
54 February 2021 (EKNZ-2021-00086). Changes in the study protocol will be immediately
55 communicated with the ethic committee. All measurements are non-invasive. Participants are
56 informed verbally about all study procedures, data policy, their right to quit this study without
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any consequences and signed a written informed consent. An additional written informed consent for stored blood and urine samples is signed. Participants are offered a state-of-the-art CV health check including clinical routine parameters as well as an exercise ECG and non-invasive CV imaging to evaluate their vascular health. All procedures are free of charge and a final medical report is available for each candidate. All participants benefit from the professional recommendations of the PA experts. The intervention group is instructed on how to perform the HIIT exercise. Temporary eye discomfort and slight headaches (in few cases) are potential negative side effects of the mydriaticum and flicker light application. In the unlikely case of persistent discomfort or pain of the eye, the patient is seen by the ophthalmologist in the University Hospital (KG) who is participating in the study.

Data are stored electronically on a database system (electronic capture system) in line with the current ethical and legal requirements. No data that could reveal the participants' identity (e.g. name, date of birth, home address) will be recorded in this database. Only the principal investigator (LS) can match the study IDs with the names of each participant. Several scientific publications as well as conference presentations are planned to report the HyperVasc study results to the scientific community. Peer-review publications will be written by investigators involved in this study. No external writers or third parties will be involved in these publications.

Authors' contributions

LS designed the study, wrote the protocol and is responsible for all assessments and the intervention. JG, JC and TH are responsible for clinical examinations and revised the manuscript. CH supports the data acquisition and revised the manuscript. AST shares his expertise in macrovascular assessments and revised the manuscript. KG is the ophthalmologist in this study and revised the manuscript. HH designed the study, supports the HyperVasc team with his clinical and academic expertise and revised the manuscript.

Funding statement

This work was supported by the [University of Basel] with the Forschungsfond grant [grant number is not applicable] to LS. The University of Basel was not involved in study design, collection, management, analysis, and interpretation of data, writing the report or the decision to submit the report for publication.

Competing interests statement

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3 All authors have no competing interests to declare.
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9 3929 without references and abstract.
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12 **Figure legend**
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14 Figure 1: Study design of the HyperVasc trial.
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16 Abbreviations: PA, physical activity; BP, blood pressure; PWV, pulse wave velocity; FMD,
17 flow-mediated dilatation; SVA, static retinal vessel analysis; DVA, dynamic retinal vessel
18 analysis; VO₂peak, peak oxygen uptake; HIIT, high-intensity interval training.
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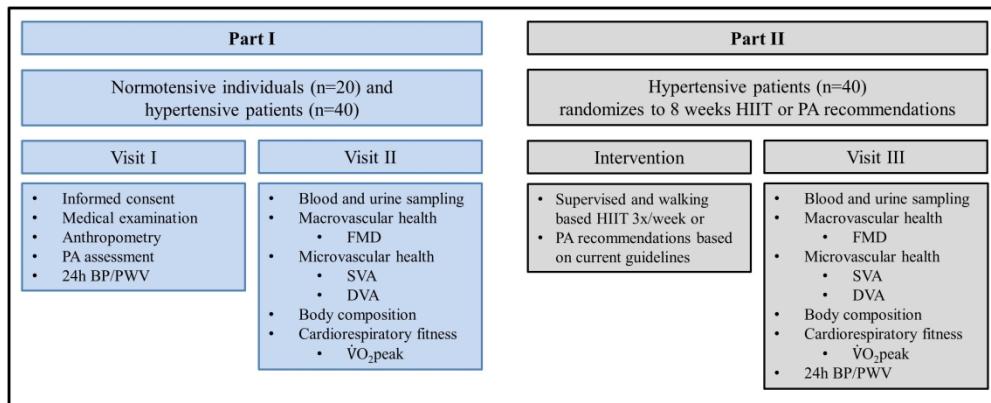
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Study design of the HyperVasc trial.

Abbreviations: PA, physical activity; BP, blood pressure; PWV, pulse wave velocity; FMD, flow-mediated dilatation; SVA, static retinal vessel analysis; DVA, dynamic retinal vessel analysis; VO₂peak, peak oxygen uptake; HIIT, high-intensity interval training.

263x107mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2 and 6
	2b	All items from the World Health Organization Trial Registration Data Set	6
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 11
	5b	Name and contact information for the trial sponsor	1 and 11
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9-11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	6 and 9
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9 and 11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6 and 9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 and 6-11
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6 and 11

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
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	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7 and 10
		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7 and 10 and N.A.
	Methods: Data collection, management, and analysis			
	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-12
		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10
	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
	Methods: Monitoring			
	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9-10

- 1 21b Description of any interim analyses and stopping guidelines, including 9-10
2 who will have access to these interim results and make the final
3 decision to terminate the trial
4
5 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and 9-10
6 spontaneously reported adverse events and other unintended effects
7 of trial interventions or trial conduct
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9 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and 9-10
10 whether the process will be independent from investigators and the
11 sponsor
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15 **Ethics and dissemination**
16
17 Research ethics 24 Plans for seeking research ethics committee/institutional review board 11-12
18 approval (REC/IRB) approval
19
20 Protocol 25 Plans for communicating important protocol modifications (eg, 11-12
21 amendments changes to eligibility criteria, outcomes, analyses) to relevant parties
22 (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
23 regulators)
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25
26 Consent or assent 26a Who will obtain informed consent or assent from potential trial 11-12
27 participants or authorised surrogates, and how (see Item 32)
28
29 26b Additional consent provisions for collection and use of participant data 11
30 and biological specimens in ancillary studies, if applicable
31
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33 Confidentiality 27 How personal information about potential and enrolled participants will 9-11
34 be collected, shared, and maintained in order to protect confidentiality
35 before, during, and after the trial
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37 Declaration of 28 Financial and other competing interests for principal investigators for 12
38 interests the overall trial and each study site
39
40 Access to data 29 Statement of who will have access to the final trial dataset, and 9-11
41 disclosure of contractual agreements that limit such access for
42 investigators
43
44 Ancillary and 30 Provisions, if any, for ancillary and post-trial care, and for 11
45 post-trial care compensation to those who suffer harm from trial participation
46
47
48 Dissemination 31a Plans for investigators and sponsor to communicate trial results to 11
49 policy participants, healthcare professionals, the public, and other relevant
50 groups (eg, via publication, reporting in results databases, or other
51 data sharing arrangements), including any publication restrictions
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54 31b Authorship eligibility guidelines and any intended use of professional 11
55 writers
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57 31c Plans, if any, for granting public access to the full protocol, participant- 9-11
58 level dataset, and statistical code
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2 **Appendices**

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Informed consent materials 32 Model consent form and other related documentation given to participants and authorised surrogates 11-12

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Biological specimens 33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable 7

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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

BMJ Open

Hypertension and retinal microvascular dysfunction (HyperVasc): Protocol of a randomized controlled exercise trial in patients with hypertension

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-058997.R1
Article Type:	Protocol
Date Submitted by the Author:	17-Mar-2022
Complete List of Authors:	Streese, Lukas; University of Basel, Department of Sport, Exercise and Health Gander, Joséphine; University of Basel, Department of Sport, Exercise and Health Carrard, Justin; University of Basel, Department of Sport, Exercise and Health Hauser, Christoph; University of Basel, Department of Sport, Exercise and Health Hinrichs, Timo; University of Basel, Department of Sport, Exercise and Health Schmidt-Trucksäss, Arno; University of Basel, Department of Sport, Exercise and Health Gugleta, Konstantin; University of Basel, Department of Ophthalmology Hanssen, Henner; University of Basel, Department of Sport, Exercise and Health
Primary Subject Heading:	Sports and exercise medicine
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	Hypertension < CARDIOLOGY, SPORTS MEDICINE, CLINICAL PHYSIOLOGY

SCHOLARONE™
Manuscripts

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3 **Hypertension and retinal microvascular dysfunction**
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13 Lukas Streese^{1*}, Joséphine Gander¹, Justin Carrard¹, Christoph Hauser¹, Timo Hinrichs¹,
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Abstract

Introduction: Hypertension is a global health care burden that affects the structure and function of the macro- and microcirculation and induces disease-specific end-organ damage. Vascular biomarkers are essential to timely diagnose this end-organ damage to improve cardiovascular (CV) risk stratification and medical decision making. Exercise therapy is an effective means to improve vascular health and reduce overall CV risk. However, it is still not clear whether high-intensity interval training (HIIT) is recommendable for patients with hypertension to reduce blood pressure, increase cardiorespiratory fitness and ameliorate vascular health.

Methods and analysis: The “Hypertension and retinal microvascular dysfunction” (HyperVasc) trial will investigate macro- and microvascular impairments in hypertensive patients compared to healthy controls to investigate hypertension-induced end-organ damage by using gold-standard methods as well as newly developed unique retinal microvascular biomarkers. In addition, this trial will investigate the reversibility of retinal end-organ damage by assessing the effects of an eight-week supervised and walking based HIIT on blood pressure, cardiorespiratory fitness as well as macro- and microvascular health, compared to a control group following standard physical activity recommendations. Primary outcome will be the arteriolar-to-venular diameter ratio. Secondary outcomes will be arteriolar and venular diameters as well as the flicker-light-induced dilation. Further outcomes will be other retinal microvascular biomarkers, flow-mediated dilation of the brachial artery as well as blood pressure, cardiorespiratory fitness, microalbuminuria, hypertensive retinopathy, and classical CV risk markers. Analysis of variance and analysis of covariance will be used to investigate group differences between healthy controls and hypertensive patients and training effects in hypertensive patients, respectively.

Ethics and dissemination: The Ethics Committee of Northwestern and Central Switzerland approved this study (EKNZ-2021-00086). All participants will give informed consent.

Registration details: The HyperVasc study was registered in February 2021 on kofam (NCT04763005) and ClinicalTrials. gov: NCT04763005.

Strengths and limitations of this study:

- The HyperVasc trial will investigate, for the first time, hypertension-related macro- and microvascular impairments by using newly developed non-invasive techniques of retinal microvascular phenotyping.

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- The results of this study will 1) improve the understanding of microvascular impairments in hypertensive patients, 2) improve the knowledge of exercise-induced macro- and microvascular remodelling, and 3) highlight the potential of retinal vessel imaging for cardiovascular risk stratification and therapy monitoring in patients with hypertension to improve medical decision making in a personalised medicine approach.
 - Generalization of the results to other patients' cohorts will only be possible with reserve.

For peer review only

Introduction

Arterial hypertension is a growing global health care burden. The number of hypertensive patients is predicted to increase globally to 60% by 2025¹. The prevalence in Europe is thought to be about 30-45%, with increasing blood pressure (BP) levels at higher age². About 40% of all annual deaths in Europe are directly related to hypertension-induced cardiovascular (CV) disease³.

Hypertension affects the structure and function of the macro- and microcirculation and leads to advanced vascular ageing. A timely diagnosis of dysfunction beyond vascular ageing allows for improved estimation of individual CV risk and more specific clinical decision making in primary and secondary CV prevention⁴. The European Society of Cardiology Working Groups on Atherosclerosis and Vascular Biology, Aorta and Peripheral Vascular Diseases, Coronary Pathophysiology and Microcirculation, and Thrombosis have recently discussed several vascular biomarkers to detect endothelial function or dysfunction⁵. The authors discussed advantages and disadvantages of macro- and microvascular assessments and highlighted the potential of retinal vessel imaging as non-invasive technique to quantify microvascular endothelial function. However, they criticised the lack of normative data and standard operating procedures for this method. We have addressed this research gap and recently published normative data and standard operating procedures for static and dynamic retinal vessel analysis⁶. Nevertheless, more clinical studies with reference values for different cohorts as well as follow-up assessments are needed to quantify benefits and the added value for CV risk stratification and potential treatment monitoring⁵.

Different non-invasive techniques to investigate the macro- and microvascular structure and function exist. Flow-mediated dilatation (FMD) is considered to be the gold standard to quantify endothelial function in the macrocirculation⁷. Blunted FMD has been shown to be predictive for CV events⁸ and all-cause mortality⁹. Each unit decrease of FMD was associated with 16% higher risk to develop hypertension¹⁰. Impaired endothelial function leads to the development of atherosclerosis by increasing arterial wall thickness and plaque formation^{11 12}. Together with markers of arterial stiffness and central haemodynamics, FMD is a frequently used vascular biomarker for the evaluation of vascular dysfunction in the macrocirculation. However, the method has not yet been implemented in clinical routine mainly due to a remaining high interobserver and day-to-day variability.

Microvascular organ damage can be investigated by performing the static (SVA) or dynamic (DVA) retinal vessel analysis, which are both non-invasive techniques and valid biomarkers of

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3 vascular health and CV risk⁶. Narrower retinal arteriolar diameter equivalents (CRAE), wider
4 venular diameter equivalents (CRVE) and a lower arteriolar-to-venular diameter ratio (AVR)
5 have been associated with a higher risk of stroke¹³⁻¹⁵, coronary artery disease¹⁶ and CV
6 mortality^{17 18}. Retinal arteriolar narrowing is predictive for the development of hypertension
7 and is associated with the severity of hypertension¹⁹⁻²¹.
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10 The method of DVA has the potential to directly and non-invasively investigate microvascular
11 endothelial function by measuring flicker light-induced dilatation (FID) over time. FID is
12 negatively associated with CV risk factors such as age^{22 23}, increased body mass^{24 25}, blood
13 pressure²⁶ or cholesterol²⁷ as well as manifest CV diseases such as diabetes²⁸ or heart failure²⁹.
14 Impaired FID seems to be predictive for non-fatal and fatal CV disease events in high risk
15 cohorts^{30 31}. Every standard deviation decrease in FID reduced all-cause mortality by up to 35%
16 in end-stage renal disease patients. The reclassification rate of additional FID was 27%
17 compared to standard care in this three-years follow-up study³⁰.
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20 We have recently established normative data and recommendations for standard operating
21 procedures for SVA and DVA⁶. In addition, we developed two new methods to improve non-
22 invasive phenotyping in the retinal microcirculation, which have not yet been applied in
23 patients with hypertension^{32 33}. The first new approach allows for the investigation of the wall-
24 to-lumen ratio in retinal arterioles and venules³². By inducing an acute standardized BP rise
25 using a defined hand-grip exercise, we are able to assess the retinal myogenic constriction in
26 addition to and as a counter regulatory mechanism of FID³³.
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29 Lifestyle interventions such as exercise, salt-reduced diet or alcohol reduction can have a
30 significant impact in lowering BP and may have additional health benefits beyond their BP
31 impact³⁴. We have recently shown that physical activity (PA) and exercise improve retinal
32 microvascular health in healthy children and adults, as well as CV risk patients³⁵. In addition,
33 regular PA is effective in reducing BP and evidence suggests that PA can reduce the risk of
34 developing de novo hypertension³⁶. A meta-analysis of 13 prospective cohort studies including
35 more than 135 000 participants confirmed a 19% risk reduction of developing hypertension in
36 individuals with high versus low PA³⁷. PA and high cardiorespiratory fitness (CRF) seem to be
37 beneficial even in hypertensive patients. A study on the combined effects of BP and PA on CV
38 mortality revealed health benefits for individuals with high versus no PA, independent of their
39 BP levels³⁸. Especially, high CRF seems to protect against vascular ageing³⁹⁻⁴¹. Hypertensive
40 patients with high CRF levels demonstrated a lower prevalence of carotid atherosclerosis.
41 High-intensity interval training (HIIT) is an effective method to increase CRF and seems to
42 have superior health benefits compared to moderate-continuous training in healthy⁴² and
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diseased populations^{43 44}. Costa et al. showed no differences between HIIT and moderate-continuous training interventions on resting BP. However, HIIT showed higher improvements in CRF compared to moderate-continuous training with potential for long-term health benefits for patients⁴⁵. The European Association of Preventive Cardiology and the Council on Hypertension of the European Society of Cardiology have recently summarised the evidence of exercise in the prevention and treatment of arterial hypertension⁴⁶. Endurance training was the first exercise priority for hypertensive patients with an expected BP lowering effect of -4.5 to -7.4 mmHg, followed by a combination of endurance and resistance training (-5.3 to -5.6 mmHg), isometric (-5.1 to -5.2 mmHg) and dynamic resistance training (-2.3 to -2.4 mmHg). However, the authors noted that the evidence for HIIT as exercise therapy to reduce blood pressure is scarce. Therefore, the HyperVasc study will investigate whether HIIT is a suitable exercise therapy for hypertensive patients to reduce BP, increase CRF and, improve subclinical retinal microvascular end-organ damage indicating overall vascular risk reduction.

Methods and analysis

Study design

The “Hypertension and retinal microvascular dysfunction” (*HyperVasc*) study consists of two parts. Part I is designed as cross-sectional study, part II is designed as randomized controlled trial. Twenty healthy and normotensive controls and 40 hypertensive patients are included in part I to investigate group differences in BP, CRF and the hypertension-induced macro- and microvascular end-organ damage. Part I is essential especially for the new methods of retinal vessel imaging to be able to analyse hypertension-induced vascular maladaptation compared to healthy controls. In part II, hypertensive patients are randomized following their baseline assessment into a HIIT group (n=20) or a control group with standard PA recommendations (n=20) to investigate the exercise effects on BP, CRF as well as the macro- and microvascular phenotype (Figure 1). In addition to vascular health, extensive phenotyping including classical CV risk markers is performed. Phenotyping details are described below. The phenotyping as well as the training intervention will take place at the Department of Sport, Exercise and Health (DSBG), Basel, Switzerland. The study is planned and conducted in accordance with the Helsinki Declaration⁴⁷. All participants have to sign a written informed consent, prior to the first assessment. The Ethics Committee of Northwestern and Central Switzerland approved this study (EKNZ-2021-00086). This study was registered on the official registry platform for research with humans in Switzerland (kofam: NCT04763005) directly after we received ethical

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3 approval. The first patient contacted us directly after the study was published on kofam. A few
4 days later we also registered our study on ClinicalTrials.gov: NCT04763005 (February 2022).
5 Due to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-nCOV-2) pandemic, all
6 assessments are conducted under consideration of the hygiene recommendations developed by
7 the Task-Force of the University of Basel based on the guidelines of the National Ministry of
8 Health (BAG).
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15 Inclusion and exclusion criteria 16

17 Men and women previously diagnosed with hypertension, receiving drug treatment for arterial
18 hypertension and controlled BP, hypertension grade I is accepted (study threshold: $\leq 159/99$
19 mmHg) as well as normotensive healthy controls (study threshold: $\leq 129/84$ mmHg) between
20 40 and 70 years of age are recruited via advertisements in local newspapers. For BP
21 categorisation, patients are measured on two separate days according to the current 2018
22 ESC/ESH hypertension guidelines⁴⁸. Exclusion criteria for both groups are any CV medication
23 (except for antihypertensive medication in the hypertensive group), history of CV, pulmonary,
24 or chronic inflammatory disease, active smoking status, body mass index ≥ 30 kg/m², macular
25 degeneration, glaucoma or any chronic eye disease, exercise-limiting orthopaedic problems,
26 high intraocular pressure (IOP) (≥ 20 mmHg) or changes in antihypertensive medication during
27 the intervention period.
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38 Anthropometry, blood pressure, physical activity and fitness 39

40 Anthropometric data are measured in the morning under fasting conditions. Height and waist
41 circumference are measured by use of standard procedures. The Inbody 720R (JP Global
42 Markets GmbH, Germany) is used to obtain body mass, body mass index, lean body mass and
43 body fat⁴⁹. Blood samples are drawn by venepuncture of the cubital fossa of the right or left
44 arm by trained staff. Urine samples are taken to measure microalbuminuria in all participants.
45 Blood and urine samples are centrifuged and stored at -80° for further analysis after data
46 acquisition has been completed successfully. BP is measured over 24 hours using the Mobil-
47 O-Graph® 24h pulse wave reflection monitor device (I.E.M GmbH, Germany) with integrated
48 ARCSolver® software. This device measures the peripheral and central haemodynamics as well
49 as the 24h pulse wave velocity (PWV) every 20 minutes during the day and every 60 minutes
50 during the night. IOP is measured with the ICare PRO (Tiolat Oy, Helsinki, Finland) rebound
51 tonometer.
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3 Self-reported PA levels are analysed using the Freiburg Questionnaire of Physical Activity⁵⁰.
4 Physical fitness is measured with an individualized bicycle ramp protocol as previously
5 described⁵¹ using the Cortex Metalyzer R 3B metabolic test system (Cortex Biophysik GmbH,
6 Leipzig, Germany) to analyse circulatory and ventilatory parameters including peak oxygen
7 uptake (VO_2peak) and maximal heart rate (HRmax). Individual exhaustion is achieved when
8 participants reach the previously defined respiratory exchange ratio cut-off value of 1.10 for
9 participants between 40-59 years of age and 1.06 for participants between 60-69 years of age⁵².
10 The individual ramp protocol is repeated on a separate day if individual exhaustion is not
11 achieved.
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20 Macro- and microvascular assessments

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22 All vascular assessments are performed in the morning under fasting conditions. Participants
23 are asked to avoid alcohol and exercise 24h prior the appointment and any food or caffeine
24 intake at the day of the appointment. Only unsweetened water and medication intake is allowed.
25 Investigators are blinded for the patients' characteristics and group allocation in the vascular
26 assessments at baseline and during image analysis of vascular parameters at the end of the
27 study.

32 Macrocirculation

33 FMD is measured with a semiautomatic and ECG-guided high resolution B-mode ultrasound
34 system (UNEX EF 38G, UNEX Corp., Nagoya, Japan) after 15 minutes of rest in a supine
35 position. Measurement takes place in a dark, quiet and temperature-controlled room. The arm
36 of the participants is abducted in a 90° angle in a relaxed position. A 10-MHz H-shaped probe
37 is used to measure the right brachial artery on a short- and long-axis. The device continuously
38 corrects the probe position during the whole procedure to generate the image with the highest
39 quality. A cuff placed at the forearm of the participants (5-10 cm distal to the probe and 1-2cm
40 proximal to the cubital fossa) increases cuff pressure for 5 minutes 50mmHg above the resting
41 BP, measured after 15 minutes of rest in a supine position. Rest diameter of the right brachial
42 artery is measured before cuff-inflation for 10 seconds. In addition, the diameter of the brachial
43 artery is measured continuously during the last 60 seconds of the inflation period and during 3
44 minutes after cuff deflation to analyse sheer stress induced vascular response.

45 The 24h PWV is analysed every 20 minutes during the day and every 60 minutes during the
46 night with the Mobil-O-Graph®, in combination with the BP measurement, as described above.

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Microcirculation

Conventional eye drops (Tropicamide 0.5%) are used to dilate the pupil of the right eye of each participant. The left eye is used in cases of local eye disease on the right eye. Images of the eye background with the optic disc in the centre using the Dynamic Vessel Analyzer (DVA®; IMEDOS Systems GmbH, Jena, Germany) and a fundus camera (450 FF; Carl Zeiss, Jena, Germany) are taken to assess retinal vessel diameters. Standard operating procedures are used to analyse CRAE, CRVE and AVR as described previously⁶ based on three high quality images with an angle of 50°. The retinal vessel microstructure, including the retinal vessel wall and the wall-to-lumen ratio is analysed based on three images with an angle of 20° and a green filter as described previously³². The oxygen saturation of the retinal microcirculation is analysed based on two images with a specific oxygen filter⁵³. A senior ophthalmologist rates the presence and severity of hypertensive retinopathy based on one high-definition image of each participant.

Retinal endothelial function is analysed with the same camera by measuring arteriolar and venular diameters over time with two protocols. The first protocol investigates neurovascular coupling using FID as a marker of retinal, and therefore, cerebrovascular endothelial function. A detailed method description can be found elsewhere⁶. The second protocol investigates the myogenic constriction of the retinal microcirculation, also known as the Bayliss effect. Participants are asked to perform a standardized handgrip exercise to increase their BP, which results in a myogenic constriction of the smooth muscles of the vessels. To standardize the BP increase, the Leonardo Mechanograph GF® device (Novotec Medical GmbH, Pforzheim, Germany) is used to test the grip strength one repetition maximum (1RM) of the left hand. The best value of three attempts is taken as guidance for the handgrip exercise. The BP is controlled beat-to-beat during the whole procedure by using the Finapres® (Finapres Medical Systems B.V., Enschede, Netherlands) device on the middle finger of the right hand. The setup has been described in detail previously³³. The second protocol starts with a 50-second rest phase. This rest phase is used to calculate the baseline diameter. After 50 seconds of rest the participants are asked to press the Leonardo Mechanograph GF® device with the left hand for 30 seconds with 30% of their 1RM. The produced power is controlled with the Leonardo Mechanography BAS v4.4 software. An acoustic signal is implemented to help the participants stay at 30% of their 1RM. A variance of 2% is tolerated. After 30 seconds at 30% 1RM, participants are verbally motivated to press as hard as possible for another 30 seconds (all-out phase) to reach a peak BP increase. A subsequent rest phase of 80 seconds is implemented to investigate the

vessel response after myogenic constriction. The vessel diameters of two arteriolar and venular vessel segments are measured continuously during the whole procedure.

Exercise intervention and control condition

Hypertensive patients are randomized to an 8-week HIIT or a control group. The exercise intervention is a supervised and walking-based HIIT (3x/week), starting with a habituation week with an intensity of 75% HRmax. In the following seven weeks, the participants will perform a HIIT based on the following protocol and with a total duration of 45 minutes per session (modified from Wisloff et al.⁵⁴): warm-up for 10 minutes at 60-70% HRmax followed by a high-intensity interval consisting of 4x4 minutes at 80-95% HRmax with 3 minutes of active recovery at 60-70% HRmax and a 10-minute cool-down at 60-70% HRmax. Heart rate will be monitored during training by Polar® H7 heart rate sensors combined with Polar® M400 watches. Sport scientists motivate the participants during the high intensity intervals and will control the heart rate of each participant during and after every training session. This training program has previously been used in CV risk patients with a high adherence and without any drop-out related due to the exercise training⁵⁵. The control group will get PA recommendations and exercise training advices based on current guidelines⁵⁶, the CRF test and the PA questionnaire. Participants in the control group document their PA behaviour in a PA diary and get a phone call after 4 weeks to evaluate their well-being.

Data management

Investigators are trained by experts in all assessments. Vascular assessments are performed by one experienced investigator to avoid inter-observer variability. Data are stored in a laboratory data base without external access with generated study IDs. Previously selected investigators have access to this database. Only the principal investigator can match names of the participants with study IDs. Data are cleaned and checked for their plausibility at the end of the study. Changes in the database are registered and controlled by an external researcher at the end of the study. This researcher is not involved in planning the study, data acquisition or analysing the data. Auditing during the data acquisition period is not planned but all study entries in the final database will be stored and are replicable at the end of the study. Interim analysis is not planned. Potential drop-outs and their reasons are collected and reported at the end of the study. The study will be stopped immediately for individual patients if any of the following adverse events should occur: adverse CV event such as angina pectoris or major adverse CV event

(MACE), musculoskeletal adverse events or acute glaucoma incidence. Adverse events will be communicated directly to the ethic committee. Drop-out participants are invited to take part in the follow-up assessment where all assessments from visit III are planned (Figure 1). Multiple imputation is used to handle missing data^{57 58}.

Randomization

A blockwise randomization is done to get equal group sizes in the HIIT and the control group. An independent research assistant draws group allocation from a locked envelope to perform randomization after baseline assessments. LS is responsible to communicate the enrolment decision to participants. Sex was the only stratification factor during the randomization process. Participants and sport scientists who supervise the intervention are not blinded for group allocation. Outcome assessors and researchers who analyse data are blinded for group allocation.

Statistical analysis

The primary outcome of this study is the AVR difference between hypertensive patients and normotensive healthy controls in the cross-sectional part (Part I) and among hypertensive patients before and after eight weeks of HIIT compared to the control group (Part II). Secondary outcomes are CRAE, CRVE, as well as arteriolar and venular retinal endothelial function. Further outcomes are arteriolar and venular retinal myogenic constriction, retinal wall-to-lumen ratio and retinal oxygen saturation as well as FMD, 24h BP, VO₂peak and microalbuminuria. Median and interquartile ranges are used to describe patients' characteristics in both parts. Boxplots are used to visualize the primary and secondary outcomes in the cross-sectional and the interventional part. Analysis of variance are used to compare AVR (and secondary outcomes) between patients and healthy peers. For the interventional part, analysis of covariance are calculated to compare AVR (and secondary outcomes) after 8 weeks of intervention between the HIIT and the control group adjusted for the corresponding values at baseline, antihypertensive medication at baseline, age, sex and ΔBP⁵⁹. Intention-to-treat principle is used as primary analysis and per protocol as secondary analysis. The statistical program R (R Foundation for Statistical Computing, Vienna, Austria, version 3.5.0.) will be used for the generation of graphs and for statistical tests with a two-sided confidence interval of 95%.

Sample size calculation

Cross-sectional approach:

Based on previous results a mean AVR difference between patients and healthy peers of 0.04 with a standard deviation of 0.04 is expected⁶⁰. To reach a power of 95% with a two-sided significance level of 0.05, a total sample size of 46 participants is needed. To reach the target power in case of missing data, based on insufficient data quality, 20 controls and 40 patients are included in this study.

Interventional approach:

An exercise-induced AVR improvement of 0.03 with a standard deviation of 0.05 is expected, based on our previous publication⁵⁵. A total sample size of 32 participants is necessary to reach a power of 95% with a two-sided significance level of 0.05. Due to possible drop-outs 40 participants in total are included to randomize these participants to 20 patients in the control and 20 patients in the exercise intervention condition. We used G*Power software 3.1.9.2 for the sample size calculation⁶¹.

Patient and public involvement statement

All methods included in this study have been used in previous trials. Participants' feedback is used to select material and methods. Participants are not involved in the study design. However, participants are asked to take part in the acquisition by communicating the trial with their families and friends. The HIIT is planned to take place at the DSBG. In single cases, the intervention can be performed at home based on participants' availability but controlled by a heart rate sensor and stored on a Polar® M400 watch. Participants will be informed about their individual results directly after their visits and about the overall study results at the end of the HyperVasc study. In addition, all participants get detailed and individualized PA and exercise training advices based on the CRF test and the PA questionnaire to optimize their daily PA behaviour.

Time plan

The acquisition started in February 2021 after the ethical approval and is still ongoing. Last patient out is planned for spring 2022. This is the first and only version of the HyperVasc study plan.

Hypotheses and potential impact

The HyperVasc trial will investigate, for the first time, the BP-induced macro- and microvascular impairments in detail by using newly developed techniques of retinal microvascular imaging. Primarily, we expect to find a lower AVR in patients with hypertension compared to healthy controls and a more pronounced arteriolar dilatation and venular constriction amongst further amelioration of the assessed retinal microvascular pathophysiology after 8 weeks of HIIT in patients with hypertension compared to standard PA recommendations. Both hypotheses will be addressed for the secondary and further outcomes. The results of this study will 1) improve the understanding of retinal microvascular impairments in hypertensive patients, 2) enhance the knowledge of exercise-induced macro- and microvascular remodelling, and 3) highlight the potential of investigating retinal microvascular end-organ damage for CV risk stratification and therapy monitoring to improve the medical decision making in a personalised medicine approach. Generalization of the results is limited since we excluded patients with CV comorbidities such as dyslipidaemia or obesity. However, we have previously examined the effects of exercise treatment in patients with multiple CV risk factors including a high prevalence of hypertension⁵⁵.

Ethics and disseminations

The Ethics Committee of Northwestern and Central Switzerland approved this study in February 2021 (EKNZ-2021-00086). Changes in the study protocol will be immediately communicated with the ethic committee. All measurements are non-invasive. Participants are informed verbally about all study procedures, data policy, their right to quit this study without any consequences and signed a written informed consent. An additional written informed consent for stored blood and urine samples is signed (supplementary file 1). Participants are offered a state-of-the-art CV health check including clinical routine parameters as well as an exercise ECG and non-invasive CV imaging to evaluate their vascular health. All procedures are free of charge and a final medical report is available for each candidate. All participants benefit from the professional recommendations of the PA experts. The intervention group is instructed on how to perform the HIIT exercise. Temporary eye discomfort and slight headaches (in few cases) are potential negative side effects of the mydriaticum and flicker light application. In the unlikely case of persistent discomfort or pain of the eye, the patient is seen by the ophthalmologist in the University Hospital (KG) who is participating in the study.

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3 Data are stored electronically on a database system (SecuTrail) in line with the current ethical
4 and legal requirements. No data that could reveal the participants' identity (e.g. name, date of
5 birth, home address) will be recorded in this database. Only the principal investigator (LS) can
6 match the study IDs with the names of each participant. Several scientific publications as well
7 as conference presentations are planned to report the HyperVasc study results to the scientific
8 community. Peer-review publications will be written by investigators involved in this study.
9 No external writers or third parties will be involved in these publications.
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17 Authors' contributions

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19 LS designed the study, wrote the protocol and is responsible for all assessments and the
20 intervention. JG, JC and TH are responsible for clinical examinations and revised the
21 manuscript. CH supports the data acquisition and revised the manuscript. AST shares his
22 expertise in macrovascular assessments and revised the manuscript. KG is the ophthalmologist
23 in this study and revised the manuscript. HH designed the study, supports the HyperVasc team
24 with his clinical and academic expertise and revised the manuscript.
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33 Funding statement

34 This work was supported by the [University of Basel] with the Forschungsfond grant [grant
35 number is not applicable] to LS. The University of Basel was not involved in study design,
36 collection, management, analysis, and interpretation of data, writing the report or the decision
37 to submit the report for publication.
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43 Competing interests statement

44 All authors have no competing interests to declare.
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48 Word Count:

49 3929 without references and abstract.
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54 Figure legend

55 Figure 1: Study design of the HyperVasc trial.
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Abbreviations: PA, physical activity; BP, blood pressure; PWV, pulse wave velocity; FMD, flow-mediated dilatation; SVA, static retinal vessel analysis; DVA, dynamic retinal vessel analysis; VO₂peak, peak oxygen uptake; HIIT, high-intensity interval training.

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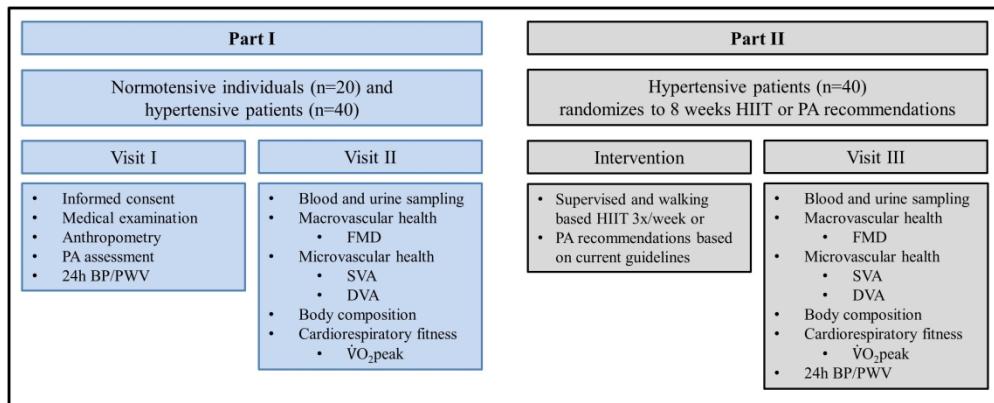
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20 Study design of the HyperVasc trial.

21 Abbreviations: PA, physical activity; BP, blood pressure; PWV, pulse wave velocity; FMD, flow-mediated
22 dilatation; SVA, static retinal vessel analysis; DVA, dynamic retinal vessel analysis; VO₂peak, peak oxygen
23 uptake; HIIT, high-intensity interval training.

24 263x107mm (300 x 300 DPI)

Anfrage zur Teilnahme an medizinischer Forschung:

Wirkung von Bluthochdruck und körperlicher Aktivität auf das Gefäßssystem (HyperVasc)

Sehr geehrte Dame, sehr geehrter Herr

Wir fragen an, ob Sie bereit wären, an unserem Forschungsvorhaben mitzuwirken.

Ihre Teilnahme ist freiwillig. Alle Daten, die in diesem Forschungsprojekt erhoben werden, unterliegen strengen Datenschutzvorschriften.

Das Forschungsvorhaben wird vom Departement für Sport, Bewegung und Gesundheit der Universität Basel unter der Leitung von Herrn Dr. Lukas Streese durchgeführt. Alle Teilnehmenden werden bei Interesse am Ende des Forschungsprojektes über die Ergebnisse informiert.

In einem Gespräch erklären wir Ihnen die wichtigsten Punkte und beantworten Ihre Fragen. Damit Sie sich bereits jetzt ein Bild machen können, hier das Wichtigste vorweg. Im Anschluss folgen dann weitere, detaillierte Informationen.

Warum führen wir dieses Forschungsvorhaben durch?

- Bluthochdruck ist ein weit verbreiteter Risikofaktor, der langfristig ernsthafte Herz-Kreislauf-Ereignisse hervorrufen kann.
- In unserem Forschungsvorhaben wollen wir den Einfluss von Bluthochdruck auf das Gefäßssystem untersuchen und herausfinden, ob Bewegungstherapie ein adäquates Mittel ist, um Gefäßschäden zu reduzieren.

Was muss ich bei einer Teilnahme tun? – Was geschieht mit mir bei einer Teilnahme?

- Form der Teilnahme: Wenn Sie sich entscheiden mitzumachen, laden wir Sie zu zwei Terminen ein, um Sie ärztlich zu untersuchen. Dazu gehört eine ärztliche Befragung zu etwaigen Vorerkrankungen, eine 24h Blutdruckmessung, eine Blutentnahme, die Abgabe einer Urinprobe, eine Messung Ihrer Körperfzusammensetzung, eine Erhebung Ihrer körperlichen Aktivität und Ihrer Fitness, sowie nicht-invasive (ohne Eingriffe in Ihren Körper) Untersuchungen Ihrer Gefäßgesundheit.
- Ablauf der Teilnahme: Beim ersten Termin, der ca. eine Stunde dauern wird, werden wir Ihren Blutdruck in Ruhe messen und Ihnen ein Blutdruckmessgerät mitgeben. Dieses Gerät misst Ihren Blutdruck im 24h Verlauf. Auf Basis dieser Untersuchungen können wir final entscheiden, ob wir Sie in unsere Studie aufnehmen können. Bei Aufnahme laden wir Sie zeitnah zu einem zweiten Untersuchungstermin ein, der ca. 2-3 Stunden dauern wird. Bei Ausschluss ist eine weitere Teilnahme leider nicht möglich.
- Besonderheit für Bluthochdruckpatienten: Personen mit einem diagnostizierten Bluthochdruck bekommen nach der zweiten Untersuchung ein begleitetes achtwöchiges Ausdauertrainingsprogram oder Bewegungsempfehlungen

5 basierend auf aktuellen Leitlinien. Anschliessend laden wir Sie erneut ein, um die
6 Eingangsuntersuchungen zu wiederholen.

7 Welcher Nutzen und welches Risiko sind damit verbunden?

8 Nutzen

- 10 Sie bekommen eine direkte ausführliche Rückmeldung zu unseren
11 Gesundheitsuntersuchungen (24h Blutdruck, Gefässgesundheit, Belastungs-EKG
12 und Leistungstest, sowie Körperzusammensetzung).
- 13 Zudem bekommen Sie von uns individuelle Bewegungs- und
14 Trainingsempfehlungen basierend auf der Leistungsdiagnostik.
- 15 Blut und Urinproben werden erst am Ende der Gesamtstudie untersucht. Diese
16 Daten können wir Ihnen erst mit einiger Verzögerung mitteilen.
- 17 Durch diese Studie kann die Diagnostik von Gefässerkrankungen, zum Wohle
18 künftiger Patientinnen und Patienten, verbessert werden.
- 19 Bluthochdruckpatienten bekommen ein professionell betreutes achtwöchiges
20 Trainingsprogramm oder weitergehende Bewegungsempfehlungen, basierend auf
21 aktuellen Richtlinien.
- 22
- 23
- 24
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26 Risiko und Belastung

- 27 Die kleinen Blutgefässe werden anhand von Fotos und Videos vom
28 Augenhintergrund untersucht. Dazu werden wir ein Auge weittröpfen. Die Gabe von
29 Augentropfen kann zu vorübergehendem „Brennen“ führen und in seltenen Fällen
30 Kopfschmerzen verursachen. Nach der Augenuntersuchung sollten Sie zu Ihrer
31 eigenen Sicherheit vier Stunden nicht aktiv am Straßenverkehr teilnehmen.
- 32
- 33

34 Mit Ihrer Unterschrift am Ende des Dokuments bestätigen Sie, dass Sie freiwillig teilnehmen und
35 dass Sie die Inhalte des gesamten Dokuments verstanden haben.

4 Detaillierte Information

1. Ziel und Auswahl

2 Unser Forschungsvorhaben bezeichnen wir in dieser Informationsschrift als *Forschungsprojekt*.
3 Wenn Sie an diesem Forschungsprojekt teilnehmen, sind Sie eine *Teilnehmerin* bzw. ein *Teilnehmer*.

4 In diesem Forschungsprojekt wollen wir untersuchen, wie Bluthochdruck auf das Gefässsystem wirkt
5 und ob Bewegungstherapie ein adäquater Ansatz ist, um durch Bluthochdruck verursachte
6 Gefässveränderungen zu reduzieren. Teilnehmen können alle Personen, die einen normalen (≤ 90
7 mmHg diastolischer und ≤ 140 mmHg systolischer Blutdruck nach 10 Minuten Ruhe in liegender
8 Position und keine Medikamente gegen Bluthochdruck) oder medikamentös gut eingestellter
9 Blutdruck (≤ 90 mmHg diastolischer und ≤ 140 mmHg systolischer Blutdruck nach 10 Minuten Ruhe
10 in liegender Position) aufweisen.

11 2. Allgemeine Informationen

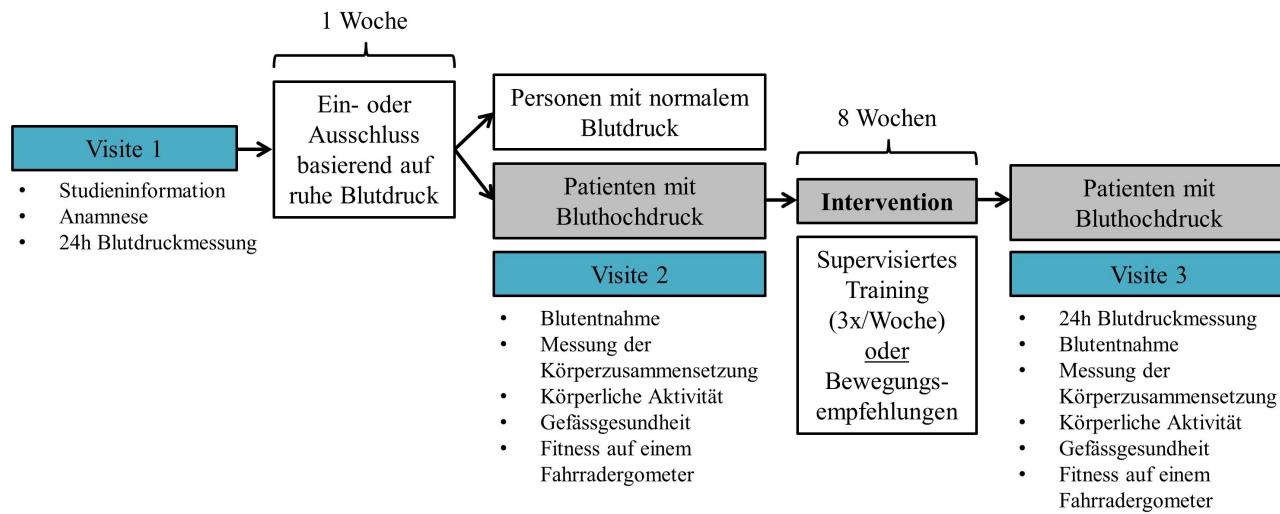
12 Bluthochdruck ist ein weit verbreiteter Risikofaktor für die Entstehung von ernsthaften Schädigungen
13 des Herz-Kreislauf-Systems. Die Auswirkungen von Bluthochdruck auf die Struktur und die Funktion
14 des Gefässsystems ist bisher nicht abschliessend untersucht. In dieser Studie werden die grossen
15 und kleinen Blutgefässer von Personen mit und ohne Bluthochdruck umfangreich jedoch nicht-invasiv
16 (ohne Eingriffe in Ihren Körper) untersucht. Diese nicht-invasiven Methoden bieten ein grosses
17 Potential für routinemässige Analysen der Gefässgesundheit als Präventionsmassnahme. Etwaige
18 Unterschiede zwischen Personen mit und ohne Bluthochdruck können das Verständnis für durch
19 Bluthochdruck verursachte Gefässveränderungen verbessern.

20 Vermehrte körperliche Aktivität, besonders in höheren Intensitäten, hat einen positiven und
21 blutdrucksenkenden Effekt. In wie weit sich die Funktion oder Struktur insbesondere der kleinen
22 Blutgefässer durch Bewegungstherapie verändert, ist bisher nicht abschliessend erforscht. Deshalb
23 werden alle Bluthochdruckpatienten zufällig einer achtwöchigen Trainingsgruppe oder einer Gruppe
24 mit individuellen Trainingsempfehlungen zugeordnet. Die Trainingsgruppe wird in dieser Zeit dreimal
25 pro Woche ein Trainingsprogramm am Department für Sport, Bewegung und Gesundheit
26 durchführen. Die individuellen Trainingsempfehlungen werden eigenverantwortlich durchgeführt.
27 Beide Gruppen werden nach acht Wochen erneut eingeladen, um die Auswirkungen des
28 Trainingsprogramms und der Bewegungsempfehlungen auf den Blutdruck und das Gefässsystem
29 zu untersuchen.

- 30
- 31 ▪ Die individuelle Dauer dieses nationalen und monozentrischen (Untersuchung findet
32 ausschliesslich in Basel statt) Forschungsprojektes beträgt ca. 1-2 Wochen für Personen mit
33 normalem Blutdruck und 10-12 Wochen für Patienten mit Bluthochdruck. Insgesamt sind 60
34 Studienteilnehmende für diese Studie eingeplant.
 - 35 ▪ Wir führen dieses Forschungsprojekt so durch, wie es die Gesetze in der Schweiz vorschreiben.
36 Ausserdem beachten wir alle international anerkannten Richtlinien. Die zuständige
37 Ethikkommission hat das Forschungsprojekt geprüft und bewilligt.

38 3. Ablauf

39 Der generelle Studienablauf ist auf der nächsten Seite grafisch dargestellt und im Detail im Text
40 erläutert. Alle Studienteilnehmende werden zunächst telefonisch oder per Mail über den generellen
41 Ablauf der Studie informiert. In diesem ersten Kontakt findet auch eine Abklärung über eine mögliche
42 Teilnahme statt. Wenn von Seiten der Projektleitung oder des Studienteilnehmenden nichts gegen
43 eine Teilnahme spricht, wird ein Termin für die Visite 1 vereinbart. Alle Untersuchungen, wie auch
44 das Training, finden am Department für Sport, Bewegung und Gesundheit statt (Eisarena Süd im St.
45 Jacob Park in Basel). Es kann sein, dass wir Sie von dem Forschungsprojekt vorzeitig ausschliessen
46 müssen. Das kann vor allem nach der Analyse der 24h Blutdruckmessung geschehen.



Ablauf Visite 1 (ca. 1 Stunde):

Zu Beginn werden wir Sie über den genauen Ablauf der Studie informieren und mit Ihnen die Einverständniserklärung gemeinsam durchgehen. Nach Ihrer Zustimmung werden wir eine kurze Befragung (Anamnese) zu etwaigen Vorerkrankungen und Risikofaktoren durchführen. Im Anschluss werden wir Ihren Blutdruck nach 10 Minuten ruhigem Liegen messen und ein Ruhe EKG aufzeichnen. Zusätzlich werden wir eine ärztliche Anamnese durchführen. Im Anschluss wird Ihnen ein 24h Blutdruckmessgerät angelegt und erklärt. Dieses Blutdruckmessgerät müssen Sie für die folgenden 24h (auch in der Nacht) tragen. Mit Hilfe dieses Gerätes wird Ihr Blutdruck in regelmässigen Abständen gemessen. Wir bitten Sie, dieses Gerät zeitnah nach Ablauf der 24h zurück an das Department für Sport, Bewegung und Gesundheit zu bringen. Nach Analyse der erhobenen Blutdruckdaten in Ruhe und aus der 24h Messung können wir final entscheiden, ob wir Sie in diese Studie aufnehmen können. Falls wir Sie nicht aufnehmen können, werden Ihre Daten gelöscht und die Studie ist für Sie beendet. Selbstverständlich übermitteln wir Ihnen dennoch gerne die Ergebnisse der 24h Blutdruckanalyse. Falls nichts gegen eine weitere Teilnahme spricht, laden wir Sie zur zweiten Visite ein.

Ablauf Visite 2 (ca. 2-3 Stunden):

In der zweiten Visite werden wir Ihnen eine kleine Menge Blut abnehmen (ca. 15ml), Ihre Körperzusammensetzung (Gewicht, Muskel- und Fettmasse) analysieren, Ihre Fitness messen und Ihr Gefäßsystem untersuchen. Das Gefäßsystem wird mit nicht-invasiven Methoden untersucht. Um die Struktur und Funktion der kleinen Blutgefäße zu untersuchen, werden wir Fotos und Videos von Ihrem Augenhintergrund machen. Für diese Untersuchung müssen wir ein Auge von Ihnen weittröpfen, das kennen Sie vielleicht von Ihrem Augenarzt. Ihre Fitness messen wir mit einem Ausbelastungstest auf dem Fahrradergometer.

Intervention (nur für Patienten mit Bluthochdruck):

Patienten mit Bluthochdruck werden nach Visite 2 entweder einer Trainingsgruppe zugeordnet oder sie erhalten individuelle Trainingsempfehlungen. Darüber entscheidet der Zufall.

Die Trainingsgruppe absolviert ein achtwöchiges Trainingsprogramm (3x/Woche), das ein geh/laufbasiertes Training mit ruhigen und intensiveren Intensitäten beinhaltet und von Sportwissenschaftlern betreut wird.

Die Gruppe mit Bewegungsempfehlungen bekommt eine individuelle Empfehlung zu ihrer körperlichen Aktivität, wird aber während der acht Wochen nicht begleitet.

Ablauf Visite 3 (ca. 2-3 Stunden und nur für Patienten mit Bluthochdruck):

Nach Abschluss der achtwöchigen Intervention laden wir Sie erneut zu uns ein, um die Messungen von Visite 1 und 2 zu wiederholen.

4. Nutzen

Wenn Sie bei diesem Forschungsprojekt mitmachen, bekommen Sie eine direkte und ausführliche Rückmeldung zu unseren Gesundheitsuntersuchungen (24h Blutdruck, Gefässgesundheit, Belastungs-EKG und Leistungstest, sowie Körperzusammensetzung). Falls Sie bei uns den Leistungstest absolviert haben, bekommen Sie von uns eine individuelle Bewegungs- und Trainingsempfehlung. Die Ergebnisse der Blut- und Urinanalyse können wir Ihnen erst mit etwas Verzögerung mitteilen. Diese werden erst am Ende der Datenerhebung analysiert (voraussichtlich im Frühjahr 2022). Zusätzlich zu dem direkten Feedback, das Sie erhalten, tragen Sie mit Ihrer Teilnahme entscheidend zur Verbesserung des Verständnisses von Bluthochdruck verursachten Gefässveränderungen bei. Mit den Erkenntnissen aus dieser Studie kann die Diagnostik von Gefässerkrankungen weiterentwickelt und verbessert werden. Alle Studienteilnehmenden bekommen eine persönliche Bewegungs- und Trainingsempfehlung. Patienten mit Bluthochdruck bekommen zusätzlich ein angeleitetes achtwöchiges Trainingsprogramm oder weitergehende individuelle Bewegungsempfehlungen, basierend auf aktuellen Richtlinien.

5. Freiwilligkeit und Pflichten

Ihre Teilnahme ist freiwillig. Wenn Sie nicht an diesem Forschungsprojekt teilnehmen oder später Ihre Teilnahme zurückziehen wollen, müssen Sie dies nicht begründen. Ihre Behandlung/Betreuung ist unabhängig von Ihrem Entscheid gewährleistet.

Wenn Sie an diesem Forschungsprojekt teilnehmen, werden Sie gebeten:

- sich an die Vorgaben und Anforderungen des Forschungsprojekts durch den Prüfplan zu halten
- sich an die Anweisungen des Studienpersonals zu halten
- die Trainingsvorgaben einzuhalten (nur für Bluthochdruckpatienten)

6. Risiken und Belastungen

Durch das Forschungsprojekt sind Sie nur geringfügigen Risiken wie einer Blutentnahme oder vorübergehendem „Brennen“ nach der Gabe von Augentropfen ausgesetzt.

7. Alternativen

Wenn Sie nicht an diesem Forschungsprojekt teilnehmen möchten, aber offen für die Möglichkeit sind, an anderen Forschungsprojekten teilzunehmen, sprechen Sie bitte mit der Projektleitung.

8. Ergebnisse

Es gibt

1. individuelle Ergebnisse des Forschungsprojekts, die Sie direkt betreffen,
2. objektive End-Ergebnisse des gesamten Forschungsprojekts.

Zu 1: Die Projektleitung wird Sie im Verlauf des Projekts über alle für Sie persönlich wichtigen neuen Ergebnisse und Erkenntnisse informieren. Sie werden mündlich und schriftlich informiert und können dann erneut entscheiden, ob Sie an dem Projekt weiter teilnehmen möchten.

Zu 2: Die Projektleitung wird Ihnen am Ende des Forschungsprojekts eine Zusammenfassung der Gesamtergebnisse zukommen lassen.

9. Vertraulichkeit von Daten und Proben

9.1. Datenverarbeitung und Verschlüsselung

Für dieses Forschungsprojekt werden Daten zu Ihrer Person und Gesundheit erfasst und bearbeitet, teilweise in automatisierter Form. Bei der Datenerhebung werden Ihre Daten verschlüsselt. Verschlüsselung bedeutet, dass alle Bezugsdaten, die Sie identifizieren könnten (Name, Geburtsdatum etc.), gelöscht und durch einen Code ersetzt werden (https://swissethics.ch/assets/Themen/akzeptierte_verschlüsselung_d.pdf). Personen, die keinen Zugang zu dieser Schlüssel-Liste haben, können keine Rückschlüsse auf Ihre Person ziehen. Die Schlüssel-Liste bleibt immer beim Projektleiter.

1 Sport- und Bewegungsmedizin
2 Departement für Sport, Bewegung und Gesundheit
3 Universität Basel, Switzerland
4 Birsstrasse 320 B, CH – 4052 Basel



Nur sehr wenige Fachpersonen werden Ihre unverschlüsselten Daten sehen und zwar nur, um Aufgaben im Rahmen des Forschungsprojekts zu erfüllen. Diese Personen unterliegen der Schweigepflicht. Sie als teilnehmende Person haben das Recht auf Einsicht in Ihre Daten.

9.2. Datenschutz und Schutz der Proben

Alle Vorgaben des Datenschutzes werden streng eingehalten. Es ist möglich, dass Ihre Daten verschlüsselt und anonymisiert, zum Beispiel für eine Publikation, übermittelt werden müssen und anderen Forschern zur Verfügung gestellt werden. Wenn gesundheitsbezogene Daten/Proben vor Ort gelagert werden, handelt es sich um eine Datenbank/Biobank für Forschungszwecke.

9.3. Datenschutz bei Weiterverwendung

Ihre Daten und Proben könnten für die Beantwortung von anderen Fragestellungen zu einem späteren Zeitpunkt wichtig sein oder später an eine andere Datenbank/Biobank in der Schweiz oder ins Ausland für noch nicht näher definierte Untersuchungen versandt und verwendet werden. Diese andere Datenbank/Biobank muss die gleichen Standards einhalten, wie die Datenbank/Biobank zu diesem Projekt.

Für diese Weiterverwendung bitten wir Sie, ganz am Ende dieses Dokuments eine weitere Einwilligungserklärung zu unterzeichnen. Diese zweite Einwilligung ist unabhängig von der Teilnahme an diesem Projekt.

9.4. Einsichtsrechte bei Kontrollen

Dieses Forschungsprojekt kann durch die zuständige Ethikkommission überprüft werden. Die Projektleitung muss Ihre Daten für solche Kontrollen offenlegen. Alle müssen absolute Vertraulichkeit wahren.

10. Rücktritt

Sie können jederzeit von dem Forschungsprojekt zurücktreten. Die bis dahin erhobenen Daten und Proben werden in diesem Fall allerdings noch verschlüsselt ausgewertet.

11. Entschädigung

Wenn Sie an diesem Forschungsprojekt teilnehmen, bekommen Sie dafür keine finanzielle Entschädigung. Es entstehen Ihnen oder Ihrer Krankenkasse jedoch auch keine Kosten durch die Teilnahme.

12. Haftung

Falls Sie durch das Forschungsprojekt einen Schaden erleiden sollten, haftet die Universität Basel (Department für Sport, Bewegung und Gesundheit), die das Forschungsprojekt veranlasst hat und für die Durchführung verantwortlich ist. Die Voraussetzungen und das Vorgehen sind gesetzlich geregelt.

13. Finanzierung

Das Forschungsprojekt wird ausschliesslich vom Forschungsfond der Universität Basel finanziert.

14. Kontaktperson(en)

Sie dürfen jederzeit Fragen zur Projektteilnahme stellen. Auch bei Unsicherheiten, die während des Forschungsprojekts oder danach auftreten, wenden Sie sich bitte an:

Dr. sc. med. Lukas Streese,
Postdoc am Departement für Sport, Bewegung und Gesundheit
Büro: St. Jakob-Arena Süd (Raum 091B) | Mittlere Allee 18 | CH-4052 Basel
Postanschrift: Birsstr. 320B | 4052 Basel | Schweiz
Tel: +41 61 207 47 51 | E-mail: hypervasc@unibas.ch

Einwilligungserklärung

Schriftliche Einwilligungserklärung zur Teilnahme an einem Forschungsprojekt

Bitte lesen Sie dieses Formular sorgfältig durch. Bitte fragen Sie, wenn Sie etwas nicht verstehen oder wissen möchten. Für die Teilnahme ist Ihre schriftliche Einwilligung notwendig.

BASEC-Nummer (nach Einreichung): 2021-00086

Titel des Forschungsprojekts: Wirkung von Bluthochdruck und körperlicher Aktivität auf das Gefäßsystem
 (Hypertension and retinal microvascular dysfunction:
 A cross-sectional and randomized controlled exercise trial - HyperVasc)

Verantwortliche Institution: Departement für Sport, Bewegung und Gesundheit
 Birsstrasse 320b, 4052 Basel

Ort der Durchführung: St. Jakob Eisarena (Süd), Mittlere Alle 18, 4052 Basel und Sportanlage in der „Grün 80“

Leiterin/Leiter des Forschungsprojekts: Dr. sc. med. Lukas Streese

Teilnehmerin/Teilnehmer:
 Name und Vorname in Druckbuchstaben:

Geburtsdatum: _____ . _____ . _____

- Ich wurde von der unterzeichnenden Prüfperson mündlich und schriftlich über den Zweck, den Ablauf des Forschungsprojekts, über mögliche Vor- und Nachteile sowie über eventuelle Risiken informiert.
- Ich nehme an diesem Forschungsprojekt freiwillig teil und akzeptiere den Inhalt der zum oben genannten Forschungsprojekt abgegebenen schriftlichen Information. Ich hatte genügend Zeit, meine Entscheidung zu treffen.
- Meine Fragen im Zusammenhang mit der Teilnahme an diesem Forschungsprojekt sind mir beantwortet worden. Ich behalte die schriftliche Information und erhalte eine Kopie meiner schriftlichen Einwilligungserklärung.
- Ich bin einverstanden, dass die zuständigen Fachleute der Projektleitung und der für dieses Forschungsprojekt zuständigen Ethikkommission zu Prüf- und Kontrollzwecken in meine unverschlüsselten Daten Einsicht nehmen dürfen, jedoch unter strikter Einhaltung der Vertraulichkeit.
- Bei Ergebnissen, die direkt meine Gesundheit betreffen, werde ich informiert. Wenn ich das nicht wünsche, informiere ich die Prüfperson.
- Ich weiss, dass meine gesundheitsbezogenen und persönlichen Daten (und Proben) nur in verschlüsselter Form zu Forschungszwecken für dieses Forschungsprojekt weitergegeben werden können. Die Projektleitung gewährleistet, dass der Datenschutz nach Schweizer Standard eingehalten wird.
- Ich kann jederzeit und ohne Angabe von Gründen von der Teilnahme zurücktreten. Meine weitere Behandlung ist unabhängig von der Teilnahme am Forschungsprojekt gewährleistet. Die bis dahin erhobenen Daten und Proben werden für die Auswertung des Forschungsprojekts noch verwendet.
- Die Universität Basel (Department für Sport, Bewegung und Gesundheit) haftet für allfällige Schäden.
- Ich bin mir bewusst, dass die in der Informationsschrift genannten Pflichten einzuhalten sind. Im Interesse meiner Gesundheit kann mich die Prüfärztin/der Prüfarzt, die Prüfperson oder die Projektleitung jederzeit ausschliessen.

1 Sport- und Bewegungsmedizin
2 Departement für Sport, Bewegung und Gesundheit
3 Universität Basel, Switzerland
4 Birsstrasse 320 B, CH – 4052 Basel



Ort, Datum	Unterschrift Teilnehmerin/Teilnehmer
Basel, _____._____	

10 **Bestätigung der Prüfperson:** Hiermit bestätige ich, dass ich dieser Teilnehmerin/diesem
11 Teilnehmer Wesen, Bedeutung und Tragweite des Forschungsprojekts erläutert habe. Ich
12 versichere, alle im Zusammenhang mit diesem Forschungsprojekt stehenden Verpflichtungen
13 gemäss in der Schweiz geltenden Rechts zu erfüllen. Sollte ich im Verlauf des Forschungsprojekts
14 von Aspekten erfahren, welche die Bereitschaft der Teilnehmerin/des Teilnehmers an dem
15 Forschungsprojekt beeinflussen könnten, werde ich sie/ihn umgehend darüber informieren.

Ort, Datum	Name und Vorname der Prüfperson in Druckbuchstaben
Basel, _____._____	Unterschrift der Prüfperson

Einwilligungserklärung für Weiterverwendung von biologischem Material (Blutproben) in verschlüsselter Form

BASEC-Nummer (nach Einreichung):	2021-00086
Titel des Forschungsprojekts:	Wirkung von Bluthochdruck und körperlicher Aktivität auf das Gefäßsystem (Hypertension and retinal microvascular dysfunction: A cross-sectional and randomized controlled exercise trial - HyperVasc)
Teilnehmerin/Teilnehmer: Name und Vorname in Druckbuchstaben:	
Geburtsdatum:	____ . ____ . ____

Ich erlaube, dass meine verschlüsselten Blutproben aus diesem Forschungsprojekt für die medizinische Forschung weiterverwendet werden dürfen. Die Proben werden im Department für Sport, Bewegung und Gesundheit gelagert und für zukünftige, noch nicht näher definierte Forschungsprojekte auf unbestimmte Zeitdauer verwendet.

Ich habe verstanden, dass die Proben verschlüsselt sind und der Schüssel sicher aufbewahrt wird. Die Daten und Proben können im In- und Ausland an andere Daten- und Biobanken zur Analyse gesendet werden, wenn diese dieselben Standards wie in der Schweiz einhalten. Alle rechtlichen Vorgaben zum Datenschutz werden eingehalten.

Ich entscheide freiwillig und kann diesen Entscheid zu jedem Zeitpunkt wieder zurücknehmen. Wenn ich zurücktrete, werden meine Daten anonymisiert und meine Blutproben vernichtet. Ich informiere lediglich die Projektleitung und muss diesen Entscheid nicht begründen.

Normalerweise werden alle Daten und Proben gesamthaft ausgewertet und die Ergebnisse zusammenfassend publiziert. Sollte sich ein für meine Gesundheit wichtiges Ergebnis ergeben, ist es möglich, dass ich kontaktiert werde. Wenn ich das nicht wünsche, teile ich es meiner Prüfperson mit.

Wenn Ergebnisse aus den Daten und Proben kommerzialisiert werden, habe ich keinen Anspruch auf Anteil an der kommerziellen Nutzung.

Ort, Datum	Unterschrift Teilnehmerin/Teilnehmer
Basel, ____ . ____ . ____	

Bestätigung der Prüfperson: Hiermit bestätige ich, dass ich dieser Teilnehmerin/diesem Teilnehmerin Wesen, Bedeutung und Tragweite der Weiterverwendung von Proben und/oder genetischen Daten erläutert habe.

Ort, Datum	Name und Vorname der Prüfperson in Druckbuchstaben
Basel, ____ . ____ . ____	Unterschrift der der Prüfperson



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item No	Item	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2 and 6
	2b	All items from the World Health Organization Trial Registration Data Set	6
Protocol version	3	Date and version identifier	10
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 and 11
	5b	Name and contact information for the trial sponsor	1 and 11
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	9-11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	6 and 9
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6

Methods: Participants, interventions, and outcomes

1	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
2	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
3	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9
4		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
5		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9 and 11
6		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6 and 9
7	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7-11
8	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1 and 6-11
9	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11
10	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6 and 11

Methods: Assignment of interventions (for controlled trials)

Allocation:

52	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
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	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7 and 10	
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7 and 10 and N.A.	
Methods: Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-12	
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10	
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	9-10	
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10	
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10	
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	9-10	

- 1 21b Description of any interim analyses and stopping guidelines, including 9-10
2 who will have access to these interim results and make the final
3 decision to terminate the trial
4
5 Harms 22 Plans for collecting, assessing, reporting, and managing solicited and 9-10
6 spontaneously reported adverse events and other unintended effects
7 of trial interventions or trial conduct
8
9 Auditing 23 Frequency and procedures for auditing trial conduct, if any, and 9-10
10 whether the process will be independent from investigators and the
11 sponsor
12
13
14
15 **Ethics and dissemination**
16
17 Research ethics 24 Plans for seeking research ethics committee/institutional review board 11-12
18 approval (REC/IRB) approval
19
20 Protocol 25 Plans for communicating important protocol modifications (eg, 11-12
21 amendments changes to eligibility criteria, outcomes, analyses) to relevant parties
22 (eg, investigators, REC/IRBs, trial participants, trial registries, journals,
23 regulators)
24
25
26 Consent or assent 26a Who will obtain informed consent or assent from potential trial 11-12
27 participants or authorised surrogates, and how (see Item 32)
28
29 26b Additional consent provisions for collection and use of participant data 11
30 and biological specimens in ancillary studies, if applicable
31
32
33 Confidentiality 27 How personal information about potential and enrolled participants will 9-11
34 be collected, shared, and maintained in order to protect confidentiality
35 before, during, and after the trial
36
37 Declaration of 28 Financial and other competing interests for principal investigators for 12
38 interests the overall trial and each study site
39
40 Access to data 29 Statement of who will have access to the final trial dataset, and 9-11
41 disclosure of contractual agreements that limit such access for
42 investigators
43
44 Ancillary and 30 Provisions, if any, for ancillary and post-trial care, and for 11
45 post-trial care compensation to those who suffer harm from trial participation
46
47
48 Dissemination 31a Plans for investigators and sponsor to communicate trial results to 11
49 policy participants, healthcare professionals, the public, and other relevant
50 groups (eg, via publication, reporting in results databases, or other
51 data sharing arrangements), including any publication restrictions
52
53
54 31b Authorship eligibility guidelines and any intended use of professional 11
55 writers
56
57 31c Plans, if any, for granting public access to the full protocol, participant- 9-11
58 level dataset, and statistical code
59
60

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	11-12 Supplement material
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	7

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.