Prognostic Impact of Physical activity patterns after percutaneous coronary intervention- PIPAP study

Study Type:	Research project involving human subjects
Risk Categorisation:	Risk category A
Study Registration:	Clintrials.gov
Sponsor:	Prof. Dr. med. Matthias Wilhelm Leitender Arzt und Zentrumsleiter Präventive Kardiologie & Sportmedizin Universitätsklinik für Kardiologie, Inselspital, Freiburgstrasse, 3010 Bern +41 31 632 8986 Matthias.wilhelm@insel.ch
Principal Investigator	Prof. Dr. med. Matthias Wilhelm
Investigated Intervention:	No intervention, activity monitoring for risk prediction
Protocol ID	If applicable, e.g. Protocol number
Version and Date:	Version 1.3 (dated 18/11/2020)

CONFIDENTIALITY STATEMENT

PROTOCOL SIGNATURE FORM

Study Title	Prognostic Impact of Physical activity patterns after percutaneous coronary intervention- PIPAP study
Study ID	If applicable

The Sponsor-Investigator has approved the protocol version 1.3 (dated 18/11/2020) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Sponsor-Investigator:

Name: Matthias Wilhelm

Date: _____ Signature: _____

TABLE OF CONTENTS

GLOSSARY OF ABBREVATIONS

ACS	*Acute Coronary Syndrome*
AE	*Adverse Event*
ASR/DSUR	*Annual Safety Repot / Development Safety Report*
BASEC	*Business Administration System for Ethical Committees*
CR	*Cardiac Rehabilitation*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
eCRF	*electronic Case Report Form*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
IPAQ-SF	*International Physical Activity Questionnaire – Short Form*
MACE	*Major Adverse Cardiac Event*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
PCI	*Percutaneous Coronary Intervention*
SAE	*Serious Adverse Event*

1 STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Prof. Dr. med. Matthias Wilhelm
Study Title	Prognostic Impact of Physical activity patterns after percutaneous coronary intervention-PIPAP study
Short Title / Study ID	PIPAP study
Protocol Version and Date	Version 1.3 (dated 18/11/2020)
Study Registration	Clintrials.gov
Study Category and Rationale	A, no intervention, only monitoring for risk prediction
Background and Rationale	Physical activity monitoring after coronary bypass grafting and other major surgeries has been found to be predictive for hospital readmission and adverse outcome. In patients after percutaneous coronary intervention (PCI) it has been found that a patient reported activity score is predictive of 3 year major adverse coronary event (MACE). It is not known whether physical activity shortly after discharge from PCI is predictive of one-year MACE. Early identification of patients at increased risk of MACE would facilitate the intensification of preventive strategies in these patients.
Risk / Benefit Assessment	Wearing an activity tracker for two weeks following hospital discharge bears no risk. Early identification of patients at increased risk of MACE would benefit these patients as they can be followed-up more closely and more emphasis can be put on adherence to medication and other preventive strategies (e.g., smoking cessation).
Objective(s)	Primary objective is the quantification of physical activity (daily steps) during the first two weeks after hospital discharge as a predictor for MACE at one year. Secondary objectives are: 1) Comparison between daily steps and objectively measured activity counts (divided in time spent in moderate-to-vigorous activity, light activity and sedentary activity), as well as patient reported activity; 2) Association of daily steps after one year with reaching targets for systolic blood pressure, low-density lipoprotein cholesterol (LDL-C), body mass index (BMI) and glycated haemoglobin (HbA1c); 3) comparison of daily steps after hospital discharge and MACE between non cardiac rehabilitation (CR), conventional hospital based CR, tele-CR and modular CR participants; 4) comparison of daily steps at one year after hospital discharge in different CR groups.
Endpoint(s)	Primary endpoint: MACE at one year after PCI. Secondary endpoints: BMI, systolic BP, LDL-C, HbA1c 12 months after PCI; daily steps and activity level two weeks and 12 months after PCI hospital discharge; proportion and patient characteristics of CR participants and non-participants
Study Design	Observational single centre study.
Statistical Considerations	Predictive value of daily steps during the first two weeks after hospital discharge is quantified by net reclassification improvement (NRI) and by increase of area under the curve (AUC) of the receiver operating characteristic curve (ROC) of a model consisting of traditional risk factors (age, sex, cardiovascular risk factors, cardiovascular history, comorbidities).
Inclusion-/ Exclusion Criteria	Inclusion criteria: Patients after PCI younger than 80 years of age who are eligible for ambulatory CR. Exclusion criteria are inability to participate in ambulatory CR (nursing home residence, stationary CR, orthopedic or neurologic impairment prohibiting physical exercise, psychiatric conditions), and staged PCI.
Number of Participants with Rationale	The sample size is based on a previous study who found a significant difference between the quartile with lowest versus highest self-reported physical activity on MACE at 3 years after PCI. Based on this, we would need 33 events to reach a significance level of 0.05 and a power of 80% in these two quartiles or 66 events in the whole sample. According to data from CARDIOBASE Bern PCI registry, we can expect 100 MACE per year in approximately 1200 patients younger than 80 years of age undergoing PCI at our centre. If we assume that

	50% of these patients are willing to participate in our study, we could recruit about 800 patients in 16 months, who will have approximately 66 MACE within one year.
Study Intervention	Patients will be provided with an activity tracker in the form of a wrist band that they should wear continuously for two weeks after hospital discharge. After 12 months, they will be asked to wear the activity tracker again for two weeks in case they attend the clinical routine check-up in our institution.
Control Intervention	None
Study procedures	Patients will receive the wrist band, the patient information sheet including informed consent (IC), the international physical activity questionnaire - short form (IPAQ-SF), and an addressed and prepaid envelope before hospital discharge. They are asked to read the patient information when arrived at home, sign the IC when willing to participate and wear the wrist band for two weeks. After that, they should complete the IPAQ-SF, send the wrist band and signed IC to our institute. Patients who do not want to participate in the study are asked to send back the activity tracker to our institution without signing the IC. Health related data and information regarding CR uptake will be derived from the clinic's patient information system for all patients who have either signed the study IC or have not withdrawn the clinics' general informed consent to further use of data for research. MACE, patient characteristics, patient history, risk factors and comorbidities will be extracted from CARDIOBASE Bern PCI registry (ClinicalTrials.gov Identifier: NCT02241291). Patients attending the clinical routine check-up after 12 months in our institution will be asked to wear the activity tracker again for two weeks.
Study Duration and Schedule	Recruitment will last for 16 months. 10/2020 First-Participant-In 04/2023 Last-Participant-Out
Investigator(s)	Prof. Dr. med. Matthias Wilhelm Leitender Arzt und Zentrumsleiter Präventive Kardiologie & Sportmedizin Universitätsklinik für Kardiologie, Inselspital, Freiburgstrasse, 3010 Bern +41 31 632 8986 Matthias.wilhelm@insel.ch PD Dr. P. Eser Forschungsleiterin Präventive Kardiologie & Sportmedizin Universitätsklinik für Kardiologie, Inselspital, Freiburgstrasse, 3010 Bern +41 31 632 4398 prisca.eser@insel.ch
Study Center(s)	Präventive Kardiologie & Sportmedizin Universitätsklinik für Kardiologie, Inselspital, Freiburgstrasse, 3010 Bern
Data privacy	Patients will be coded and code key will be stored in secure place.
Ethical consideration	Many studies have found a strong association between physical activity and survival. Some recent studies with patients after major surgery have found daily steps/physical activity level to be a strong predictor for MACE after hospital discharge. If this can be confirmed in patients after PCI, then step monitoring will be an easy, cheap and unintrusive routine clinical assessment to identify patients at high risk for MACE, who consequently can be followed-up more closely.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

Association of step/activity count on hospital readmission

Number of steps during the three last days of hospital stay after coronary artery bypass grafting has been found to be the strongest predictor for 30-day cardiac rehospitalisation.(1) Likewise, in patients hospitalised for decompensated heart failure, physical activity within the first week after hospital discharge was predictive of 30-day hospital readmission.(2) Slow gait speed measured in the home setting one month after acute myocardial infarction (MI) was found to be associated with a hazard ratio of 1.76 (95% confidence interval 1.08-2.87) for hospital readmission or death within one year when adjusted for age and sex.(3) In older patients (>75 years) after acute MI, functional mobility at hospital discharge was the strongest predictor for 30-day hospital readmission.(4) Interestingly, in-hospital walking activity was found to be more predictive of 30-day rehospitalisation than in-hospital activities of daily living function in older acutely ill patients.(5) Furthermore, self-reported physical activity significantly improved the prediction of 3-year MACE over traditional risk factors in patients after elective PCI.(6)

Step counting versus activity counts

Current recommendations for cardiovascular patients by the European Society for Cardiology include 150 min a week of moderate intensity or 75 min a week of vigorous intensity aerobic PA or an equivalent combination thereof.(7) In the 1960, a Japanese pedometer company launched the 10,000 steps per day promotion, which has since been found to be an appropriate recommendation.(8, 9) In older adults, a recommendation of 7,000-10,000 has been suggested to be appropriate. In order to reach an activity level that corresponds to at least moderate, a cadence of at least 100 steps/min has to be reached.(for review see Tudor-Locke et al.(10)) Therefore, half an hour of moderate activity corresponds to at least 3000 steps. However, there are no evidence based recommendation with regard to intensity level in older adults.(9) In fact, daily step count has been found to be associated with disease severity in patients with hypertrophic cardiomyopathy, while activity counts were not.(11)

Step/activity counts during CR

According to a study by Savage and Ades,(12) over 60% of patients at a mean of 36 days after PCI or CABG were sedentary (performing less than 5,000 steps/day), and less than 15% performed more than 10,000 steps/day. Activity counts per minute increased by 12% from the first to the last week of a 4-6-week cardiac rehabilitation (CR) programme.(13) In a randomised controlled trial with patients after recent MI randomised to a home-based CR programme or usual care, patients of the intervention group increased their activity counts per minute by 89% over the 3-month CR while there was no change in activity counts in the control group.(14) Both of these studies were based on small sample sizes and included a maximum of 30 patients. Sixty-four CR patients were randomised to a 3-month tele-rehabilitation programme provided by a hospital, a community health care centre or a call centre. Steps per day increased by 34% from the beginning of the tele-rehabilitation programme to one year, with no differences between the three CR providers.(15)

Tele-rehabilitation vs. centre-based CR

A recent review found tele-rehabilitation to be more successful at reducing hospital readmission and adverse events due to cardiovascular events and also for adhering to physical activity recommendations than conventional CR.(16) However, from many articles included in this review it was not clear whether tele-rehabilitation was implemented in phase II or phase III rehabilitation. A telerehabilitation programme after phase II CR in CAD patients was found to further increase exercise capacity and to reduce hospital readmission during one year follow-up by trend.(17) An older review of 2010 found no differences between home- and centre-base rehabilitation with regard to quality of life, mortality and rehospitalisation, nor cost-efficiency.(18) However, a more recent study has found tele-rehabilitation to be less cost-efficient than conventional rehabilitation.(19) More recent studies comparing tele-rehabilitation vs. centre-based conventional ambulatory rehabilitation in phase II are rare. There is one ongoing RCT in phase II

aiming at including and randomising 300 CAD patients.(20) Similar results were found for tele-rehabilitation compared to conventional CR with regard to motivation for keeping a healthy lifestyle, depression, anxiety and quality of life in 136 randomly assigned cardiac patients.(21) A non-randomised observational study has compared 24 tele-rehabilitation patients with 53 matched patients performing conventional CR during a later time period and has found similar results for physical activity assessed by questionnaire and quality of life.(22)

Risk prediction for major adverse cardiovascular event (MACE)
For patients with cardiovascular disease many instruments are available to calculate a risk score in order to estimate a patient's risk for death or reoccurring events. The RISK-PCI Score can be used for prediction of one-year adverse cardiovascular events in STEMI patients after PCI.(23) The GRACE score allows an in-hospital mortality risk assessment of patients with acute myocardial infarction as well as mortality risk assessment for up to 3 years.(24) It takes into account age, heart rate, systolic blood pressure, creatinine, abnormalities of ECG or cardiac enzymes, and signs of heart failure. The SMART risk score predicts the 10-year risk for recurrent vascular events in patients with previous cardiovascular disease.(25) Additional to age, sex, systolic blood pressure and smoking status, it takes into account history of cardiovascular disease and diabetes, as well as laboratory results of lipid status, kidney function and inflammation.

Based on the predictive value of daily steps for risk prediction found in some recent studies in various patient groups after surgery, we aim to assess the value of daily steps in patients with recent PCI in improving currently used risk assessment tools for MACE. Further, we aim to monitor whether patients enrolling in CR have higher step counts and fewer MACE than those not enrolling in CR, and whether there is a difference with regard to step counts in patients enrolling in different types of CR (conventional hospital-based CR, tele-CR, module-based CR).

3 STUDY OBJECTIVES AND DESIGN

3.1 Primary objective and hypothesis

Quantification of physical activity (daily steps) during the first two weeks after hospital discharge as a predictor for MACE at one year.

Hypothesis I: Daily steps measured during the first two weeks after hospital discharge from PCI is a significant independent predictor additional to traditional risk factors for MACE at one year after PCI.

Secondary objectives and hypothesis

1. Comparison between daily steps and objectively measured activity counts (divided in time spent in moderate-to-vigorous activity, light activity and sedentary activity), as well as patient reported activity:

   Hypothesis I: Objectively monitored activity counts two weeks after hospital discharge is significantly associated with daily step counts and self-reported activity level

   Hypothesis II: Predictive value of daily step count during the first two weeks after hospital discharge is significantly better than the predictive value by patient reported physical activity for MACE at 12 months.

2. Association of daily steps after one year with reaching targets for systolic blood pressure, low-density lipoprotein cholesterol (LDL-C), body mass index (BMI) and glycated haemoglobin (HbA1c):

Hypothesis I: *Patients with higher daily step counts during the first two weeks after hospital discharge have higher achievement rates of target levels at 12 months for blood pressure, body weight, blood lipids, and blood sugar.*

3. Comparison of daily steps after hospital discharge and MACE between non cardiac rehabilitation (CR), conventional hospital based CR, tele-CR and modular CR participants.

   Hypothesis I: Tele-rehabilitation and conventional CR patients achieve higher daily step counts (corrected for age, risk factors and comorbidities) at two weeks after PCI than patients who decline any form of CR.

   Hypothesis II: Tele-rehabilitation and conventional CR patients a lower risk of MACE within one year than patients who decline any form of CR

4. Comparison of daily steps at one year after hospital discharge in different CR groups.

   Hypothesis I: Tele-rehabilitation is not inferior to conventional ambulatory cardiac rehabilitation (CR) in increasing daily steps from two weeks after PCI to 12 months after PCI

3.2 Primary and secondary endpoints

Primary endpoint: Occurrence of MACE within 12 months after PCI
Secondary endpoints: BMI, systolic BP, LDL-C, HbA1c and daily steps two weeks and 12 months after PCI; proportion and patient characteristics of CR participants and non-participants

3.3 Study design

This is a monocentric open label explorative study (with primary objective to assess the predictive value of daily steps for MACE). Patients will be asked to wear an activity tracker for two weeks following hospital discharge. Patients who participate in any form of CR in our institution and attend the routine check-up 12 month after PCI in our institution will be asked to wear the activity tracker again for two weeks.

3.4. Study intervention

Patients will be informed about the study by the prevention team (advanced nurse practitioners) usually on the day of discharge from PCI during the routine visit by this team to inform patients about the different options of CR. Patients will be provided with an activity tracker in the form of a wrist band, the patient information sheet including informed consent (IC), the IPAQ-SF and an addressed and prepaid envelope. They are asked to read the patient information when arrived at home, sign the IC when willing to participate and wear the wrist band continuously for two weeks after hospital discharge. After that, they should send the wrist band, the filled in IPAQ-SF and signed IC in the provided envelope to our institute. If they are unwilling to participate, they can send the activity tracker back straight away. Patients attending the clinical routine check-up after 12 months in our institution will be asked to wear the activity tracker again for two weeks.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

Approximately 800 consecutive patients after PCI who are informed about different forms of CR are recruited for this study.

Study inclusion criteria:

- 18-79 years of age;
- eligible for ambulatory CR (not living in nursing home, not enrolling in stationary CR).

Exclusion criteria:

- Staged PCI;
- previous participation in this study;
- inability or contraindications to undergo CR (nursing home residence, stationary CR, orthopedic or neurologic impairment prohibiting physical exercise, psychiatric conditions)
- inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc..

4.2 Recruitment, screening and informed consent procedure

Consecutive patients who are eligible for ambulatory CR are seen by the prevention team (nurse practitioners) usually on the day of hospital discharge from PCI and will be informed about the different forms of CR and the study.

All eligible patients will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participants to make an informed decision about their participation in the study. The participants can consider their participation and decide upon participation during the first week after hospital discharge. Additionally to the patient information sheet and the IC form, the activity tracker in the form of a wrist band, the IPAQ-SF and an addressed and prepaid envelope will be handed out before hospital discharge. They are asked to read the patient information when arrived at home, sign the IC when willing to participate and wear the wrist band continuously for two weeks after hospital discharge. After that, they should send the wrist band, filled-in IPAQ-SF and signed IC in the provided envelope to our institute.

Each participant will be informed that if they lose the activity tracker or it is lost with the mail, they are not held reliable for the loss. Each participant will be informed that the participation in the study is voluntary and that he or she may withdraw from the study at any time and that withdrawal of consent will not affect his or her subsequent medical assistance and treatment.

The participant will be informed that his or her medical records may be examined by authorised individuals other than their treating physician.

The formal consent of a participant, using the approved consent form, will be signed by the participants at home and sent back with the questionnaire and activity tracker. The participants are not submitted to any study procedures other than wearing the activity tracker.

The consent form will be signed and dated by the investigator or his designee when the form arrives at the Inselspital. A copy of the signed informed consent will be sent back to the study participant. The consent form will be retained as part of the study records.

4.3 Study procedures

For each patient the study duration is two weeks during which the activity tracker is worn. Patients who complete their yearly follow-up at our institute are asked to wear the activity tracker again for

two weeks when they come to the follow-up visit.

Patient recruitment will last for 16 months, with first participant in in October 2020, last patient recruited in February 2022 and last follow-up in April 2023.

4.4 Withdrawal and discontinuation

Data gathered until withdrawal of consent will be used in coded form. Wearing the activity tracker again after 12 month is voluntary. MACE data derived from CARDIOBASE registry is subject to the CARDIOBASE registry consent, in case of withdrawal of consent for CARDIOBASE MACE and patient related data from this registry will not be used. Health related data from the clinic's patient information system will not be used if patients withdrawal the study IC and the clinic's general informed consent.

5 STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan and sample size calculation

Predictive value of daily steps during the first two weeks after hospital discharge is quantified by net reclassification improvement (NRI) and by increase of area under the curve (AUC) of the receiver operating characteristic curve (ROC) of a model consisting of traditional risk factors (age, sex, cardiovascular risk factors, cardiovascular history, comorbidities).

Descriptive statistics are used to quantify and characterise the populations who choose conventional hospital based CR, tele-rehabilitation, and modular CR in terms of number, age, sex, medical history, cardiovascular risk factors and comorbidities. MACE at one year follow-up and daily steps during the first two weeks after hospital discharge will be compared between the CR and non CR participants using multivariate modelling adjusted for potential confounding factors. Further, for patients who perform their yearly routine follow-up visit at our centre, data on body mass index (BMI), systolic blood pressure (BP), low-density lipoprotein cholesterol (LDL-C) and smoking cessation will be derived from the clinic's patient information system and compared between different forms of CR. Also, daily steps after 12 months from patients who volunteer to monitor steps again will be quantified for the different CR groups and tested between the groups if sufficient data can be gathered. The same will be done for changes in daily steps between the first two weeks after hospital discharge and at 12 months.

Sample Size:

Based on a study on nearly 9000 PCI patients, physical activity level assessed by the Duke Activity Status Index (DASI) questionnaire found a 4.8-fold increase in future risk of incident major adverse cardiac events at 3 years in the quartile with lowest DASI compared to the highest quartile.(6) The DASI score reclassified 15% of patients ($P<0.001$) beyond traditional risk factors in predicting future MACE.(6) In the approximately 6500 patients with obstructive CAD, the adjusted HR (adjusted for traditional risk factors and history of heart failure and peripheral arterial disease) for MACE in the lowest DASI quartile compared to the highest quartile was 2.66 (95% CI 2.16 to 3.27). According to this relative hazard, 33 events would be needed to reach a significance level of 0.05 and a power of 80% in these two quartiles. For the whole sample this would be 66 events. According to data from CARDIOBASE, in the 10 years from 2009-2018 1083 (8%) of patients younger than 80 years had a MACE between 7 and 365 days after PCI, which corresponds to approximately 100 MACE per year. During the last 3 years (Oct 2015 to Oct 2018), 3683 patients younger than 80 years were recruited for CARDIOBASE, which equates to approximately 1200 potential study patients per year. If we assume that 50% of these patients are willing to participate in our study (wear an accelerometer for 2 weeks after discharge), we could recruit about 600 patients per year, of whom approximately 48 (8%) will have a MACE within 12 months following PCI. To reach 66 MACE we will need to recruit 825 patients which will require

a recruitment period of approximately 16 months.

Statistical analyses will be performed by Dr. Prisca Eser (CAS in statistics of the University of Bern) using the software R.

5.2. Handling of missing data and drop-outs

CARDIOBASE has very few missing cases for MACE, therefore, for MACE, a complete case analysis will be done. Activity data will be used when at least 7 days of 12 h/day (during day time) recording are available. Otherwise, these patients will be allocated to a non-compliant group for which patient characteristics will be summarised and compared to the compliant group. Patients of the non-compliant group will not be used for the analysis of the primary endpoint. For secondary outcomes, missing data will be imputed by multiple imputation.

In case of a large number of non-compliant patients (>50), additional patients will be recruited (if necessary recruitment period will be extended).

6 REGULATORY ASPECTS AND SAFETY

6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

6.2 (Serious) Adverse Events

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

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

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

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

Relationship	Description
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible

Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

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

Reporting of SAEs (see ClinO, Art. 63)

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

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

Follow up of (Serious) Adverse Events

Describe the follow up procedures of participants terminating the study with reported ongoing (S)AEs until resolution or stabilisation.

6.3 (Periodic) safety reporting

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

6.4 Radiation

No Radiation involved.

6.5 Pregnancy

Pregnancy is not a contra-indication for wearing an activity tracker.

6.6 Amendments

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

Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29).

A list of substantial changes is also available on www.swissethics.ch.

A list of all non-substantial amendements will be submitted once a year to the competent EC together with the ASR.

6.7 (Premature) termination of study

Provide a statement that the Sponsor-Investigator and any other competent authority may terminate the study prematurely according to certain circumstances, e.g:

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise, or
- Early evidence of harm or benefit of the experimental intervention

Upon regular study termination, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

Please refer to www.swissethics.ch for a template concerning the notification of completion, discontinuation or interruption of the clinical trial.

Describe what happens to the biological materials and health-related data at the end of the study (e.g. all biological materials and health-related data are anonymised upon end of data analysis).

If the study also requires a FOPH approval or includes investigations involving unsealed or sealed radioactive sources, the study leader shall submit to the FOPH a final report including all information of relevance for radiological protection, in particular a retrospective dose estimation, within a year of completing or discontinuing the study. Routine nuclear medicine examinations involving authorised radiopharmaceuticals are exempt from these reporting requirements.

6.8 Insurance

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

7 FURTHER ASPECTS

7.1 Overall ethical considerations

The impact on patients by wearing the activity tracker is minimal and therefore of negligible ethical concern. Patients will benefit in that they can see (if they so wish) their daily steps and compare them with recommendations. The benefit to future patients will be that if proven predictive for MACE, daily steps after PCI discharge will provide an easily measurable and valuable parameter for improved follow-up care of PCI patients.

7.2 Risk-benefit assessment

No risks are involved with wearing an activity tracker (wrist band).

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

Nurses of the prevention team at the Department of Cardiology, Inselspital, will be trained in how to inform patients about this study and provide them with the study information and IC-form. Further, corresponding with routine clinical practice at the Inselspital, they will inform patients about the three different forms of CR and will recruit patients for CR. Data from activity trackers will be downloaded from devices upon their return from patients and uploaded into Redcap by

appropriately trained personnel at the unit for Preventive Cardiology and Sports Medicine of the Inselspital.

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

8.2 Data recording and source data

Data from the activity trackers will be downloaded and stored in Redcap. Questionnaires on physical activity will be manually entered into Redcap.

At the end of the study, data from this study will be merged with data from Cardiobase PCI registry, namely data on patient anthropometrics, cardiovascular history, indication for and interventions of the index PCI, comorbidities and cardiovascular risk factors, and MACE at one year follow-up. Data on choice of CR and compliance with CR and health related data will be available from the clinical data base of the unit for Preventive Cardiology and Sports Medicine of the Inselspital.

8.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number. The participant identification list will be stored by Prof. Dr. med. M. Wilhelm, principal investigator of this study but not involved in data acquisition. Redcap data banks are stored on a hospital (for clinical and activity data) or university (for questionnaire data) server and regularly backed up. Password access is provided to Dr. P. Eser and Dr. T. Marcin from the research group of the unit for Preventive Cardiology and Sports Medicine of the Inselspital. If patient data will be passed on to third parties, it will be coded. No identifiable patient data will be passed on to third parties.

8.4 Retention and destruction of study data and biological material

All study data are archived for 10 years after study termination or premature termination of the study.

9 MONITORING AND REGISTRATION

Monitoring will be performed after activity trackers have been returned by the first 50 patients, and at the end of the study. The monitoring will be performed by Dr. D. Herzig, Institute for Diabetology, Endocrinology, Nutrition Science and Metabolism of the Inselspital Bern.

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

Funding is provided by a grant from the Swiss Heart Foundation (FF19075) to the PI.

10 REFERENCES

1. Common Terminology Criteria for Adverse Events (CTCAE)
https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

2. Declaration of Helsinki
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
3. Federal Act on Data Protection (FADP)
https://www.admin.ch/opc/en/classified-compilation/19920153/index.html
4. Human Research Act (HRA)
https://www.admin.ch/opc/de/classified-compilation/20061313/index.html
5. International Conference on Harmonization (ICH) E6(R2) Guideline for Good Clinical Practice
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf
6. International Conference on Harmonization (ICH) E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf
7. Ordinance on Clinical Trials in Human Research (ClinO)
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Appendix 1: Schedule of assessments

Time (hour, day, week)	Hospital discharge	1-14 days after hospital dischare	14 to 30 days after hospital discharg	12 months after hospital discharge
Oral and written patient information	Handed out to patients by the nurses of the prevention team			
Written consent		Dated and signed by patients	Sent to study management, dated and signed by PI	
Inclusion-/ exclusion criteria	Checked by the nurses of the prevention team			
Medical history				From Cardiobase
Participant characteristics				From Cardiobase
Procedures				From Cardiobase
Questionnaire		At CR entry examination or at patients‘ homes		
Sampling		2 weeks activity tracking		2 weeks activity tracking

Please amend and expand the above schedule according to the specific study.