**Study Protocol for non-Drug- and non-Medical Device Studies**

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|   |                                                          | Prof. Dr. med. Axel Haverich, Dept. of Cardiac, Thoracic, Transplantation and Vascular Surgery |
| 2 | Sub-Investigators (Acad. title, name, affiliation)      | Dr. Sven Haufe, Institute of Sports Medicine and Institute of Clinical Pharmacology
|   |                                                          | Dr. med. Arno Kerling, Institute of Sports Medicine |
| 3 | Statistician (Acad. title, name, Affiliation)            | Dr. Dietmar Böthig, Dept. of Cardiac, Thoracic, Transplantation and Vascular Surgery |
| 4 | Title of Study                                           | Effects of a physical activity intervention on metabolic syndrome severity in employees from the Volkswagen AG. |
| 5 | Medical Condition                                        | Metabolic syndrome |
| 6 | Study Characteristics (Check all that apply)              | [X] prospective  [ ] retrospective
|   |                                                          | [X] therapeutic  [ ] observational
|   |                                                          | [ ] diagnostic  [ ] biobank/biomarker study
|   |                                                          | [ ] prophylactic |
|   |                                                          | [X] monocentric  [ ] multicentric
|   |                                                          | [X] open-label  [ ] blind or [ ] double-blind
|   |                                                          | [X] parallel group comparison  [X] randomized
|   |                                                          | [ ] single arm  [ ] cross-over
|   |                                                          | [ ] ionizing radiation (StrSchV)  [ ] X-rays (RöV)
|   |                                                          | [ ] other: |
| 7 | Intervention (If not applicable note: n.a.)              | experimental group: supervised physical exercise training
|   |                                                          | control group: waiting-control group
|   |                                                          | duration of intervention per patient: 6 months |
|   |                                                          | Based on data from initial exercise tests, activity questionnaires, and medical history the intervention group will get individual instructions with recommendations aimed to perform 150 min of physical activities per week. Heart rates during exercise sessions will be monitored with the aim of physical activities at moderate-intensity. The exercise group is equipped with an activity monitor wearing at the hand of the non-dominant arm (Forerunner 35, Garmin, Germany). Participants will be asked to wear the monitor throughout the intervention
period and be familiarized to use the device. Data will be recorded continuously when the activity monitor is attached. In addition preset or self-defined activities (e.g. cycling, cardio-training, walking outdoor and walking indoor) can be started and stopped. Additionally all participants will be asked to install a self-designed smartphone application “Rebirth active” (d.velop AG, Gescher, Germany) on their mobile phone to receive information about the study in general, individual training goals, recommended heart rates for endurance activities, tips for increased physical activity in everyday life, and supervisor contact details. Based on activity monitor data and personal communications participants receive feedback and adaptations for their further training schedule during the meetings with the exercise scientist once monthly. The supervising exercise scientist will search for fitting training facilities around the participant’s home and at the workplace (e.g. gyms, sport classes, rehabilitation courses) to help participants to increase physical activity in everyday life.

| Vulnerable Subjects | [] children  
|                     | [ ] pregnant or lactating women  
|                     | [ ] individuals > 75 years of age  
|                     | [ ] patients in palliative care  
|                     | [ ] legally non-competent individuals due to acute illness  
|                     | [ ] legally non-competent individuals due to chronic disease  
|                     | [ ] imprisoned or otherwise legally detained individuals  
|                     | [ ] nursing home inhabitants  

### Key Inclusion Criteria
(Mandatory: age/sex)
- women and men  
- ≥ 18 years  
- diagnosis of ≥ 3 of 5 criteria of the metabolic syndrome according to the AHA/NHBLI

### Key Exclusion Criteria
- current participation in occupational health program  
- acute or chronic infections  
- oncological diseases  
- joint replacements or any surgery within the last 6 weeks  
- pregnant or breast feeding women  
- any condition that precludes realization of an exercise intervention.

### Key Procedures
- exercise testing’s  
- venous blood sampling from an brachial vein  
- body composition  
- questionnaires

### Objective(s)
The metabolic syndrome (MetS) is a clustering of different abnormalities, increasing the risk for the development of cardiovascular and metabolic diseases, and cardiovascular mortality. Beside the prognostic disease and mortality risk, the MetS has been shown to be related to more absent workdays due to illness, productivity loss, and higher health-care costs. The MetS is therefore not only a health-related but also a relevant socioeconomic issue, particularly in ageing societies in whom employees are expected to work at higher ages. Several studies have tested the impact of physical activity programs on anthropometric and metabolic parameters. However, data for the effectiveness of regular exercise on metabolic syndrome severity and associated changes in work ability are sparse. In addition, whether physical activity-induced improvements in health-related (mental and physical) outcomes are similarly associated with changes in ability to work depending on an employees work area is
unclear. The evaluation of a population at risk covering different areas of work, (including shift work, blue- and white collar-work) will help to judge whether our personalized and telemonitoring-supported intervention might be feasible and effective to improve disease risk and indices of workplace productivity arising from metabolic syndrome conditions.

Therefore, the aim of the study was to test the hypothesis that a 6-month lifestyle intervention, focusing on exercise training with individualized telemonitoring-based supervision, will result in improvements of MetS severity as well as work- and health-related outcomes among company employees.

### 13 Outcome(s)

| primary endpoint: | metabolic syndrome severity as assessed with a metabolic-z-score (MetS-z-score) |
| key secondary endpoint(s): | work ability, exercise capacity, health-related quality of life, body composition, adherence to the activity intervention |
| assessment of safety: | any adverse or unexpected event was documented for any enrolled subject and descriptively analyzed |

### 14 Statistical Analysis

**Efficacy/ Aim**
The primary aim of the study is to test whether a 6-month supervised and telemonitoring-supported physical activity intervention will result in improvement of metabolic syndrome severity in company employees. The study will have a randomized-controlled design with a waitlist-control group.

**Description of the primary endpoint accuracy analysis and population:**
For analysis of the primary outcome an Analysis of Covariance model (ANCOVA) will be used with the change of the MetS-z-score (6 months-baseline) as response variable. Explanatory variables are gender, the MetS-z-score at baseline and the study group (intervention- vs. control). The intervention is successful, if the lower mark of the two-sided 95% confidence interval is bigger than 0.

To test for within-group differences from baseline to end of intervention a two-sided Students T-Test for paired samples will be applied. Univariate associations between parameters will be tested using Pearson’s correlation coefficient. The type-I-error is set to 5% (two-sided).

For all outcomes the analysis will be carried out according to the intention-to-treat (ITT) principle, including all randomized subjects. Missing values at the end of the 6 months intervention will be conservatively replaced by the baseline observation carried forward method to avoid an overestimation of the effect through drop-outs.

**Safety:**
Any adverse, serious adverse or unexpected event will be documented, descriptively analyzed, and compared between study groups.

**Secondary endpoint(s):**
For secondary outcomes the same analysis method will be used as described for the primary outcome. For dichotomic endpoints a logistic regression will be used and adjusted for the same co-variables. 95%-confidence interval will be calculated for all secondary endpoints.

### 15 Sample Size

| to be assessed for eligibility: | n = 400 |
| to be assigned to the trial: | n = 312 |
| Study Title: Effects of a physical activity intervention on metabolic syndrome severity in employees from the Volkswagen AG.  
Synopsis Version: 1.0 from 31.05.2017  
Principal Investigator: Prof. Dr. med. Uwe Tegtbur |
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<td><strong>16 Sample Size Justification</strong></td>
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| **17 Trial Duration** | recruitment period (months): 6 months  
first participant in to last participant out (months): 18 months |
| **18 Discussion of Perceived / Expected Risks and Benefits** | Specific risks in this study include exercise testing and venous blood sampling. During exercise testing there is a theoretical risk of cardiac arrhythmia. Any blood sampling has a certain risk of infection. We expect benefits for cardiovascular, metabolic and mental health due to the intervention. Because we will perform exercise testings and blood samplings in as standardized fashion according to current guidelines we believe that the expected benefits will outweigh the risk of the intervention. |
| **19 Data Monitoring Committee** | [ ] yes  
[X] no |
| **20 Feasibility of Recruitment** | The recruiting of volunteers for the physical activity program will take place at the Volkswagen factory in Wolfsburg by internal informative events and internal advertisement. The number of employees in this factory is all in all about 70.000 employees. Due to the expectedly positive effects of the event and the degree of esteem of training to improve health and well-being, we are not expecting any problems referring to the recruitment. We expect that the planned 400 volunteers will be recruited. |
| **21 Participation Fee**  
(Amount in EUR) | Not intended |
| **22 Participating Centres** | Volkswagen factory in Wolfsburg (lower saxony) |
| **23 Funding/ Role and Responsibilities** | Funding: Audi BKK health insurance and the German Research Foundation through the cluster of excellence “REBIRTH”  
The funder of this study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit for publication. |
| **24 Previous IRB Submission(s)** | First application |

Name and Signature(s) of Principal Investigator(s)  
Hannover, 01.06.2017  
Place, Date